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MYOCARDIAL CIRCULATION AND THE BILIARY TRACT: EXPERIMENTAL OBSERVATIONS USING THE ELECTROPOLAROGRAPH

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IN 1909 Babcock[2] published his classic paper citing several cases of heart disease with angina pectoris which were benefited by the removal of a diseased gall bladder. Fitz-Hugh and Wolferth[9] and others have reported similar results. Breyfogle,[4] Walsh,[25] and Tennant and Zimmerman[23] have all pointed out the statistical frequency of coexistent gall bladder and coronary artery disease. The belief that biliary tract disease can affect adversely the myocardial circulation has retained considerable popularity for many years. Possible physiologic mechanisms for such an effect have given rise to much speculation and an appreciable volume of experimental study.

The first experiments suggesting a possible gall bladder–heart relationship were reported by Carlson and Luckhardt[5] in 1921 when they demonstrated that stimulation of intestinal viscera causes cardiac inhibition in frogs and salamanders. In 1926, Anrep and Seagall[1] reported that stimulation of the peripheral vagus nerve caused constriction of the coronary arteries. It is scant wonder then that Osler is said to have cited instances in which a patient died suddenly during gallstone colic and to have attributed this phenomenon to reflex vagal stimulation or that von Bergmann[3] believed that gall bladder disease, hiatal hernia, or gastric distention could cause anginal attacks due to reflex coronary vasoconstriction.

Ravdin[19] in 1942 reported that he was able to produce anginal pain in two patients by distending the common bile duct, but previously Zollinger[28] had been unable to produce such pain by gall bladder or common duct distention in 6 patients.

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Many attempts have been made to prove or disprove the gall bladder–heart relationship using the electrocardiograph. Wakefield[24] was able to produce ECG changes by distending the gall bladder at surgery, but the changes were unpredictable. Hodge and Messer[13] were unable to produce ECG changes by distending the gall bladder at surgery or the common duct after surgery. However, they reported[14] that after production of a coronary occlusion in the dog, abnormalities of the RS-T segments occurred consistently with gall bladder distention. Wechsler[26] reported in 1954 that consistent ECG changes could be produced in dogs by gall bladder distention only if a myocardial infarction had been produced 2 to 5 days previously and then only if the dogs were not anesthetized during the distention.

Measurement of coronary blood flow has been used by several investigators to study this problem. Gilbert[10, 11] used the Rein stromuhr to measure coronary artery blood flow and reported that stimulation of abdominal organs decreased the flow. This effect was eliminated by atropine or vagus section. Eckenhoff[8] measuring coronary flow with a bubble flowmeter was unable to confirm Gilbert's results as was Winbury[27] using a rotameter. As Gregg[12] has pointed out, these methods use a severed or dissected coronary artery. The nervous control of such a vessel might well be abnormal. In 1952 Cullen,[6] using Na_{24} clearance from the myocardium as a measure of myocardial circulation, reported that distention of the biliary tract reduced myocardial circulation through vagal pathways.

This paper will present electropolarographic studies of the myocardial oxygen availability in the dog, as they pertain to this problem of a relationship between the biliary tract and the myocardial circulation. The electropolarographic method has particular merit for this study since it is unnecessary to disturb the coronary vessels to obtain very sensitive measurement of changes in oxygen availability of the myocardial tissue.

METHODS

The principle of polarography has been known and used for many years, but it was first used for physiologic studies in the brain by Davies and Brink[7] in 1942. They showed that the oxygen tension of an unknown solution may be measured by a platinum electrode acting as the cathode and recording the current flow between this and a nonpolarizable anode. Provided that the voltage is maintained constant at 0.6 volts, the current flow is proportional to the oxygen tension of the solution. Since tissue is not a solution, actual quantitative measurements have not been accurately obtained, but changes from a base line with changes in myocardial oxygen are rapid and sensitive. This method has been used in the skin by Montgomery,[17] in the brain by Meyer,[16] and in the myocardium by Sayen[20-22] and Husni.[15] A simple diagram of the circuit is shown in Fig. 1. In practice considerable electronic filtration has been added to filter high frequency output associated with activation of the heart without decreasing the sensitivity.

We use 0.008 inch (No. 32 gauge) platinum wire as the cathode. This is coated with Teflon, except for the terminal 2 mm. The reference nonpolarizable anode is a silver wire or small plate freshly plated with silver chloride before using. It is placed in the subcutaneous tissue in any convenient location. When such platinum electrodes are placed in the myocardium of a dog and the current is recorded on a direct-writing oscillograph, a base line is established with the animal breathing room air. Changes in myocardial tissue oxygen are rapidly recorded with rise or fall from this base line. If breathing of a high percentage of oxygen is instituted, a rapid and steep rise occurs in the tracing which quickly falls back to base line levels when room air breathing is resumed (Fig. 2). Conversely if 12 per cent oxygen is used, a fall from the base line occurs. When a coronary artery is clamped resulting in the electrode recording from an infarcted area of the myocardium, a fall from the base line is noted and no rise will occur with 100 per cent oxygen breathing (Fig. 3). This is further evidence that only oxygen change is being measured by the electrode.

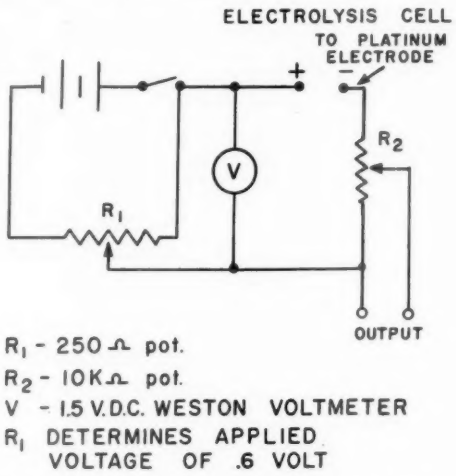

Fig. 1.—The electropolarographic circuit.

A series of mongrel dogs were anesthetized with chloralose or pentobarbital sodium anesthesia. The choice of anesthetic is important since the barbiturates are generally accepted to be vagus nerve depressants. Hence, the majority of the dogs in the first group and all the dogs in the second group were anesthetized with intravenous chloralose which has no such effect.

Respiration was maintained by a mechanical positive pressure respirator which could be attached to an oxygen supply as desired. Blood pressure was measured by a catheter in the femoral artery and recorded on a direct-writing oscillograph with a strain gauge.

The chest was opened by a midline sternum-splitting incision. The pericardium was opened widely and sutured to the wound edges to form a cradle for the heart and thus to prevent excessive motion during respiration. One or more of the previously described platinum electrodes were placed in the myocardium of the left ventricle and the silver–silver chloride anode was placed in the subcutaneous tissue of the chest wound. The electrode was tested for oxygen sensitivity by oxygen breathing (Fig. 2).

Once the proper functioning of the electrodes was ascertained, a midline abdominal incision was made and the gall bladder and common duct were visualized. In some instances a catheter was inserted in the proximal common bile duct and the entire biliary tract distended forcibly with saline. In other instances the gall bladder alone was distended after ligation of the cystic duct.

Fig. 2.

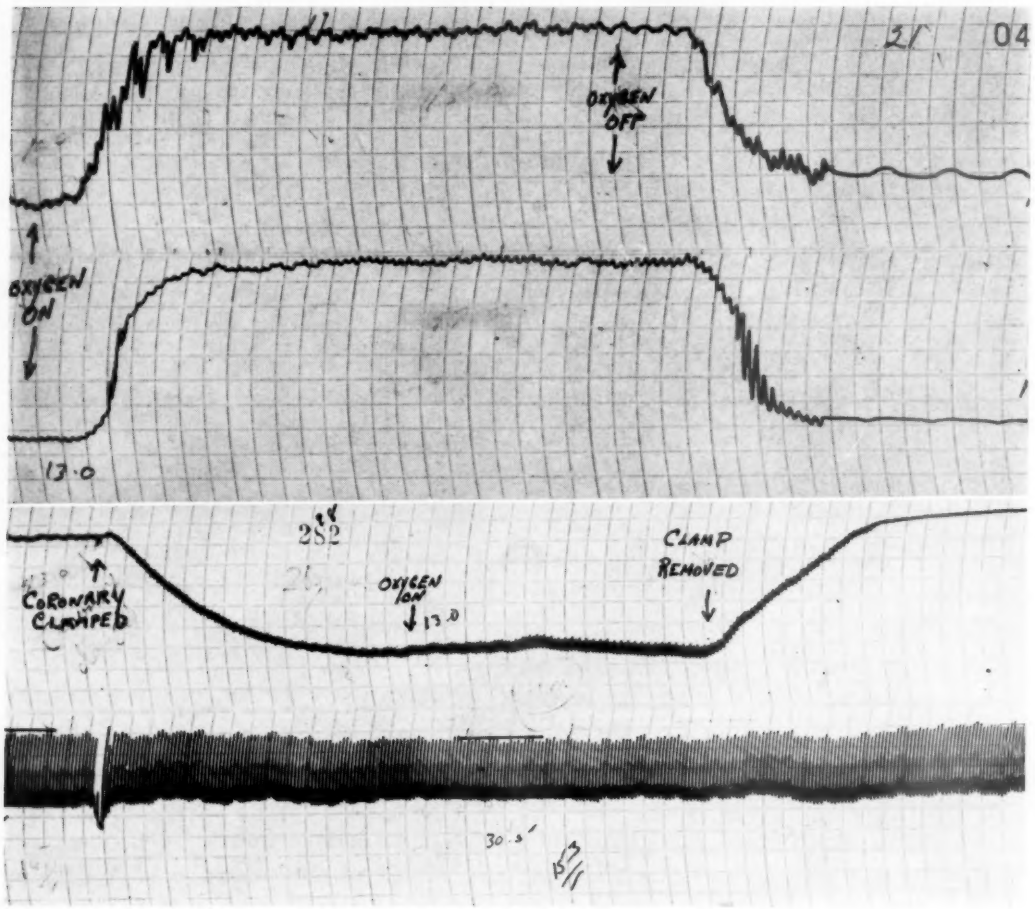

Fig. 3.

Fig. 2.—Tracings from two platinum electrodes in a dog's myocardium. Note steep rise from base line with oxygen breathing and fall back to base line with return to room air breathing.

Fig. 3.—Electropolarographic tracing from the dog's left ventricle *(above)* and blood pressure tracing from the femoral artery (*below*). Note fall from base line when coronary artery supplying the area is clamped and lack of response to oxygen breathing.

In addition to these maneuvers, the gall bladder was pinched, squeezed, and traumatized in all instances. Hence in recording the results, the term "stimulation" has been used since in each dog several methods were applied. The results in this group of eight dogs are shown in Tables I and II.

A second group of 5 dogs was similarly prepared. In addition, an apparatus modified after that described by Lamsen for maintaining constant blood pressure was utilized. As seen in Fig. 4, warmed canine plasma in a reservoir

is connected by a large catheter placed through the femoral artery to the dog's aorta. The large carboy containing compressed air at any desired pressure acts to maintain the animal's blood pressure at a corresponding level by increasing or decreasing the circulating blood volume. In each dog the sino-auricular node was crushed and a cardiac pacemaker was attached to the ventricle. This satisfactorily maintained the pulse at a constant 150 per minute.

Once a predetermined constant blood pressure and heart rate was established, exactly the same procedure as in the first group of dogs was followed. The results are shown in Table III.

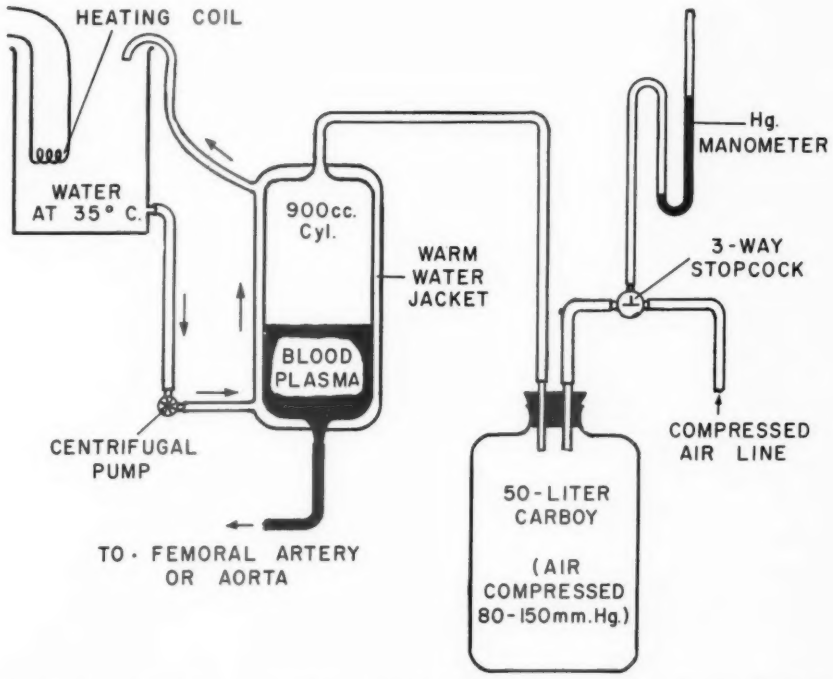

Fig. 4.—Apparatus for maintaining constant blood pressure in Group II dogs.

RESULTS

In the first group of dogs many changes in electropolarography were obtained. An example of one type of result is plotted in Fig. 5. The myocardial oxygen is recorded as millimeters of rise or fall of the electropolarogram from the base line established at room air breathing prior to oxygen breathing or biliary tract stimulation. The mean blood pressure is recorded in millimeters of mercury. Table I shows the results of stimulation on the electropolarogram and mean blood pressure in the 8 dogs of the first group. Periods of stimulation causing no significant change in blood pressure or electropolarogram are not included in Table I, but are included in Table II.

From Tables I and II, we can see that, except for two instances, no change has occurred in the myocardial electropolarogram independent of a corresponding change in the blood pressure. The pulse seemed to bear no constant relationship to electropolarographic change within the ranges observed. Minor

TABLE I. EFFECT OF GALL BLADDER STIMULATION ON MYOCARDIAL ELECTROPOLAROGRAM AND MEAN BLOOD PRESSURE

DOG NUMBER	ELECTROPOLAROGRAPHIC RISE WITH OXYGEN BREATHING (MM. RISE FROM BASE LINE)	ELECTROPOLAROGRAPHIC RESPONSE TO STIMULATION [MM. RISE (+) OR FALL (−)]	MEAN BLOOD PRESSURE RESPONSE TO STIMULATION [MM. RISE (+) OR FALL (−)]
1	+28	+10	+20
		+39	+22
		−10	−10
2	+40	−10	−12
		−22	−19
3	+35	−10	−25
		− 9	−12
		− 7	−20
4	+42	+3	+12
		− 2	−22
		+ 9	− 8
5	+40	+37	+26
		+ 9	+ 8
		+32	+10
6	+28	−11	−23
		+22	+28
		+ 4	−11
7	+35	−22	− 7
		−35	−30
8	+40	− 3	− 5
		−10	− 6

TABLE II. TYPES OF CHANGE OCCURRING IN MYOCARDIAL ELECTROPOLAROGRAM AND MEAN BLOOD PRESSURE WITH GALL BLADDER STIMULATION

TYPE OF CHANGE	NUMBER OF OCCURRENCES	PER CENT OF TOTAL
No significant change in blood pressure or electropolarogram	17	45
Blood pressure increased, electropolarogram increased	7	18
Blood pressure decreased, electropolarogram decreased	12	32
Blood pressure decreased, electropolarogram increased	2	5

changes due to pulse rate could be obscured by the greater changes obtained with blood pressure variation but this is not noted in the 45 per cent where no change in either occurred. In two instances, the electropolarogram increased slightly while the blood pressure dropped a few millimeters. This occurred in each case as the result of the final stimulation of a series in which the dog had previously reacted in the more usual manner.

No significant difference could be detected between those dogs anesthetized with pentobarbital sodium and the chloralose group.

In the second group of dogs where blood pressure and pulse rate were maintained at constant values, results were obtained in each case similar to the tracing shown in Fig. 6. Here we see that in Dog 13 with the mean blood pressure maintained at 165 ± 5 mm. Hg and the pulse at 150 per minute, the electropolarographic tracings from three electrodes in the left ventricle

TABLE III. EFFECT OF GALL BLADDER STIMULATION ON MYOCARDIAL ELECTROPOLAROGRAM WITH CONSTANT PULSE* AND BLOOD PRESSURE

DOG NUMBER	ELECTROPOLAROGRAPHIC RISE WITH OXYGEN BREATHING (MM. RISE FROM BASE LINE)	ELECTROPOLAROGRAPHIC RANGE AFTER STIMULATION [MM. RISE (+) OR FALL (−) FROM BASE LINE]	RANGE OF MEAN BLOOD PRESSURE AFTER STIMULATION
9	26	0	71-75
		0 to +1	73-74
		0 to +3	70-75
10	35	−3 to +1	86-90
		0 to −2	88-90
		−1 to +3	89-90
		+1 to −3	88-89
11	16	0 to +2	93-102
		0 to +2	92-95
		0 to +1	93-94
12	35	0 to −3	130-136
		0	130-132
		0 to −2	130-134
13	45	+2 to −1	166-169
		0 to −2	163-165
		+1 to −2	160-164

*Pulse in all instances maintained at 150 per minute by cardiac pacemaker.

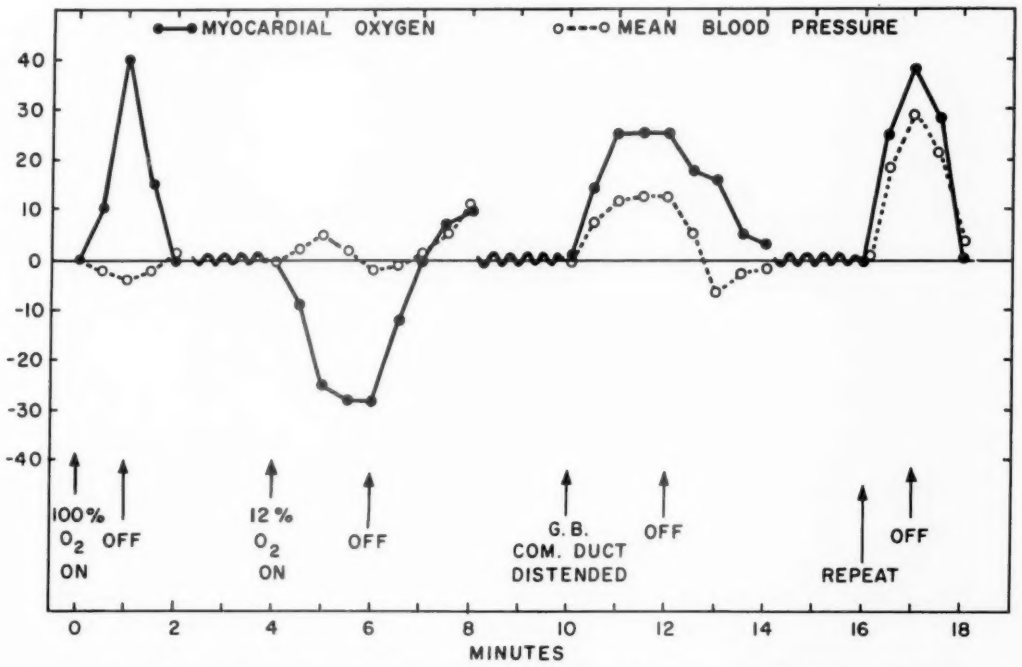

Fig. 5.—Results in a dog of first group. Note marked rise in electropolarogram with 100 per cent oxygen breathing and fall with 12 per cent oxygen breathing. No significant blood pressure change is observed. With biliary tract distention the electropolarogram rises, but in each case the blood pressure has a parallel rise. (Electropolarographic measurement in mm. rise from base line.)

show no significant change with gall bladder distention. Similar results were obtained at each blood pressure range and are shown in Table III. These results demonstrate that, when blood pressure and pulse are maintained at constant levels, no significant change occurs in myocardial oxygen due to

biliary tract stimulation. We feel that the very slight changes in electropolarography shown in Table III are not significant in view of the marked sensitivity of the instrument as shown in the response to oxygen breathing and to changes

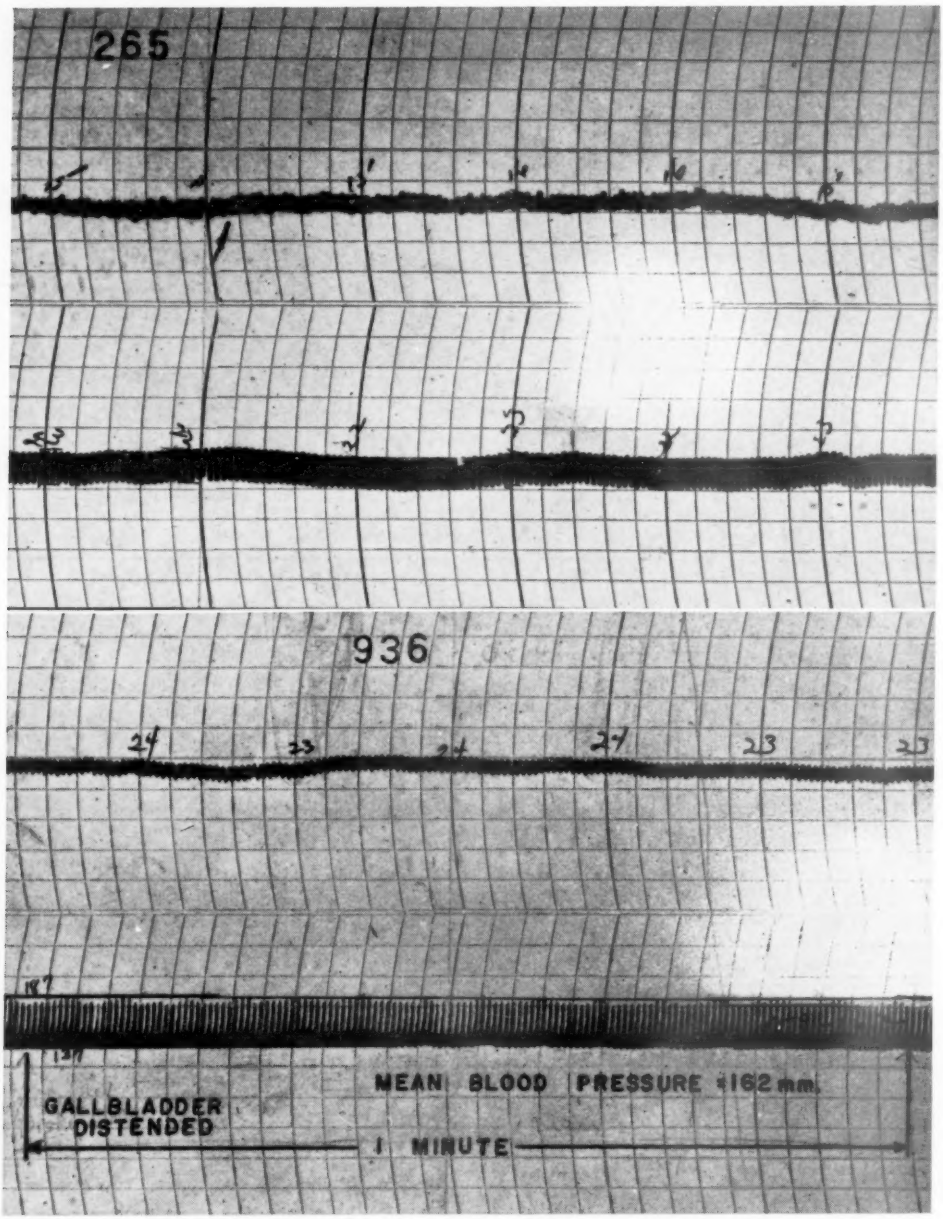

Fig. 6.—Result of gall bladder distention for one minute on the electropolarogram from three areas in the left ventricle (*upper three tracings*). Blood pressure (*lower tracing*) and pulse rate maintained at constant levels (Dog 13).

with blood pressure demonstrated in Table I for the first group of dogs. Dog 11 was tested with 40 per cent oxygen which accounts for the smaller rise during oxygen breathing than in the others tested with 100 per cent oxygen.

DISCUSSION AND CONCLUSION

From the data presented, we find no evidence that distention or trauma of the gall bladder or biliary tract produce any change in the myocardial tissue oxygen independent of change in the blood pressure or pulse. Since variation in myocardial tissue oxygen must be related to change in the coronary circulation, we conclude that no significant change in coronary artery flow occurs. This casts doubt on the existence of a viscero-vagal-coronary constrictor mechanism as postulated by Gilbert,[10, 11] Cullen,[6] and others. It is of interest that recently Okinaka[18] stated that vagus stimulation causes coronary artery vasodilatation. Our results have failed to demonstrate that biliary tract stimulation produces this effect. We can conclude then that, whether or not the vagus has vasomotor effect on the coronary arteries, it is unlikely that stimuli arising in the biliary tract can produce such an effect in the anesthetized dog.

It has been suggested by Hodge and Messer[14] and others that any effect on the myocardium by gall bladder distention takes place only when myocardial ischemia is already present. In the second group of dogs, measurements were carried out in Dog 9 and Dog 10 at blood pressure levels sufficiently low to cause myocardial ischemia. There is no indication that biliary tract stimulation in these two dogs with some myocardial ischemia caused any change in myocardial oxygen (Table III). Hodge and Messer's conclusions were drawn from electrocardiographic findings after ligation of a coronary artery. It is certainly possible that such ECG findings may relate to increased myocardial ischemia caused by the blood pressure fall which occurred rather than to a change in myocardial circulation caused by the gall bladder distention initiating a vagal coronary constriction.

In view of our findings, it seems unlikely that biliary tract surgery undertaken solely because of true angina or myocardial insufficiency is ever justified. However, if such surgery is indicated for other reasons, our findings would suggest no contraindication. In fact, this evidence that trauma to the gall bladder or biliary tract does not cause coronary constriction and myocardial ischemia may make the surgeon feel somewhat more secure when he is compelled to operate for such conditions as gangrenous cholecystitis or common duct stone in patients with myocardial insufficiency. Provided that normal blood pressure is maintained and the patient is well oxygenated at all times, there seems to be no evidence that the necessary operative trauma to the biliary tract can cause coronary constriction and increased myocardial ischemia.

SUMMARY

1. Electropolarographic measurements of changes in myocardial tissue oxygen have been used to study any change in myocardial circulation that might be instituted by distention or stimulation of the biliary tract.

2. Changes in myocardial tissue oxygen can be produced by such distention or stimulation when corresponding changes in blood pressure and heart rate occur.

3. No change in myocardial tissue oxygen can be demonstrated due to such biliary tract stimulation that is independent of change in the pulse or blood pressure.

4. These findings cast doubt on the existence of any direct vagal coronary constrictor or dilator mechanism that can be initiated by stimulation of the biliary tract and suggest only indirect effect due to blood pressure and heart rate variations.

5. It is suggested that biliary tract surgery for the sole purpose of improving angina or coronary insufficiency should not be done, but that, when such surgery is necessary for other reasons, no evidence is presented that trauma to the biliary tract at surgery will initiate any dangerous myocardial circulatory change if pulse and blood pressure are kept in normal range.

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THE CONSEQUENCE OF REPEATED INFUSIONS OF POTASSIUM IN ACUTE COMPENSATED HYPOVOLEMIA

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IN studying the problem of transfusion-induced cardiac arrest, toxic concentrations of potassium were found to occur in bank blood.[6] During hemorrhagic hypotension, animals are extremely sensitive to injected potassium[9, 11]; renal function is depressed by hypotension,[8] and potassium excretion is thus reduced. Gelhorn[4] considers hemorrhage as one of the best stimuli for liberation of epinephrine. Epinephrine induces glycolysis in the liver with concomitant release of prodigious quantities of potassium. This mechanism also accounts for the liberation of potassium from the liver during hypercapnea.[3] Hypoxia acts directly on the liver and brings about a sudden release of potassium sufficient to cause heart block in the dog.[8] During shock, anoxia liberates potassium from cell breakdown, and changes in membrane permeability account for further release.[9] Shock rarely occurs during clinical surgery. The more common situation is a hypovolemia which is unrecognized because the blood loss has not been of a magnitude sufficient to produce a change in vital signs. A loss of 20 to 30 per cent of the circulating blood volume may occur before any change in arterial pressure occurs.[7] When the compensating mechanisms responsible for homeostasis have maintained the vital signs, the condition is referred to as compensated hypovolemia. Although vital signs remain unchanged, these patients tolerate further blood loss poorly. An experiment was designed to study potassium tolerance and blood pressure responses in animals with compensated hypovolemia.

METHODS AND MATERIAL

Healthy adult mongrel dogs were divided into three groups: normovolemia, mild hypovolemia, and moderate hypovolemia. Each animal was anesthetized with pentobarbital (30 mg. per kilogram) and an endotracheal tube inserted. All of the femoral vessels and the right jugular vein were exposed. A polyethylene cannula was inserted into the right femoral artery and connected to a mercury manometer. Cannulae were inserted into the left femoral artery and vein. In all groups, 100 c.c. of arterial blood was withdrawn and 100 c.c. of bank blood (potassium concentration of 25 mEq. per liter) was slowly infused via the femoral vein. Arterial and venous pressures were recorded after the 100 c.c. of blood was withdrawn and again after 100

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c.c. was replaced. This procedure was repeated 10 times. At the end of this time, a blood sample was taken and the serum potassium concentration measured. Control animals were normovolemic. For mild hypovolemia, 100 c.c. of blood was withdrawn and the pressure allowed to return to the prebleeding level before bleeding and retransfusion. For moderate hypovolemia, 200 c.c. of blood was first withdrawn; the vital signs were also allowed to return to normal before bleeding and retransfusion. Normovolemic and hypovolemic dogs were then bled and transfused as described above. Five animals were used in each group, a total of 15 animals.

RESULTS

Figs. 1 and 2 show the changes in plasma K and pressure under the experimental conditions. The values plotted are the averages for all four experiments. The normovolemic animal is able to clear the infused hyperkalemic blood completely in a short period. The dogs with a mild hypovolemia do not handle the potassium as well as the control group. In moderate hypovolemia, toxic potassium levels were reached in each animal at the conclusion of the tenth run. The arterial pressure remained stable in Group I, but showed some fluctuations in Groups II and III during the experiment, but never to levels associated with clinical shock.

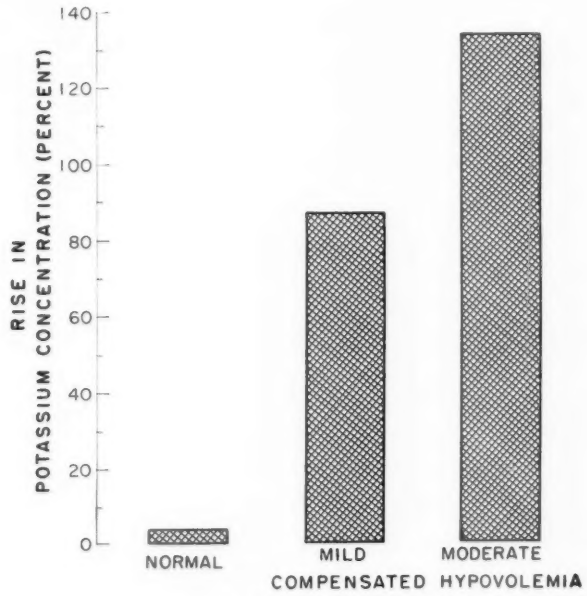

Fig. 1.—The rise in serum potassium concentration above control values is shown. The average pretransfusion level was 4.2 mEq. per liter for the 15 dogs. Average posttransfusion levels were 4.4, 7.4, and 9.8 mEq. per liter in normovolemia, mild hypovolemia, and moderate hypovolemia, respectively.

DISCUSSION

The results point out the danger of waiting for changes in vital signs to replace blood. Ebert and co-workers[2] have pointed this out previously and demonstrated that, when the compensatory mechanisms finally fail, marked pressure drops suddenly occur, making rapid massive transfusion necessary. In a

previous publication,[6] the hazard of massive transfusion during hypotension was demonstrated. The renal mechanism for potassium removal is depressed during shock.[9] These experiments illustrate that removal of potassium from the blood is impaired in acute compensated hypovolemia, even though blood pressure is maintained. Therefore, the tolerance for hyperkalemic bank blood is appreciably impaired. After repeated transfusions of bank blood, toxic levels of potassium can be reached unless the blood volume is promptly and quantitatively restored. A slight fall in blood pressure is likely to follow a transfusion of hyperkalemic blood when a compensated hypovolemia exists. This fall in pressure may be interpreted as undertransfusion. Further transfusion will then lead to overtransfusion and a continued fall in arterial pressure[10] will set a vicious cycle into action. Monitoring the venous pressure eliminates the tendency to transfuse when arterial pressure drops during overtransfusion. Exact measurements of blood loss by the conductivity method[7] allows for immediate and accurate replacement and obviates the hazards described.

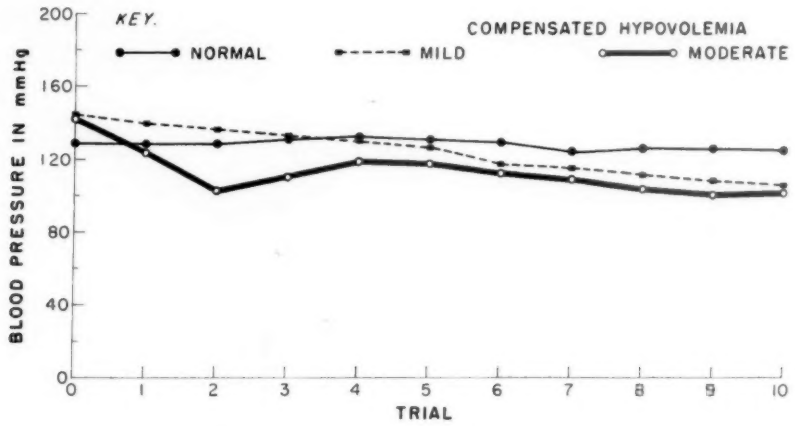

Fig. 2.—Changes in blood pressure during the transfusions are shown. There is at no time a drop in pressure to levels associated with clinical shock.

The clinical counterpart of this experiment happens regularly in the operating room. A patient loses blood as surgery progresses; this is inadequately replaced even though repeated transfusions are given. His vital signs do not change, or fluctuate minimally. The hypovolemia is not recognized until a marked drop in pressure occurs, necessitating rapid transfusion at the time he might be most sensitive to potassium. This situation can precipitate a sudden cardiac arrest as is indicated in a previous publication.[6] A loss in the potassium clearing ability in the animal with "compensated" hypovolemia regularly occurs, and its occurrence must be guarded against and avoided by maintaining the normovolemic state.

SUMMARY AND CONCLUSIONS

Compensated hypovolemia after small hemorrhages has been produced in the dog. Transfusions with hyperkalemic blood during this compensated

hypovolemia causes an elevation in serum potassium. The experiment was designed to show that repeated large transfusions in clinical patients might not be tolerated if hypovolemia is allowed to develop. It indicates that patients with compensated hypovolemia might not clear the potassium load imposed upon them by repeated transfusions of hyperkalemic bank blood.

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PRIMARY CARCINOMA OF THE GALL BLADDER

Presentation of Seventy Cases From the Rhode Island Hospital and a Cumulative Review of the Last Ten Years of the American Literature

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PRIMARY CARCINOMA of the gall bladder remains an almost uniformly lethal neoplasm. In spite of medical and surgical advances in recent years that allow hitherto impossible radicality in the extirpation of malignant tumors, this disease stands as a stumbling block, defying not only efforts toward surgical cure but also early diagnosis and effective palliation. And yet, paradoxically, because of its relation to pre-existing gall bladder disease, it offers one of the most effective therapeutic approaches to malignancy known—that of prophylaxis.

Since its description by Maximillian de Stoll[61] in 1777 (or 1771, according to some authorities), more than 4,000 cases have been documented in the world literature. Most of these are incorporated in series of less than 100 cases from any one institution. Taken as single series, these reports lack statistical significance. More than 2,000 cumulative cases, including many of the early series, were analyzed by Arminski[1] in 1949, and this represents the latest large review of the disease in this country.

It is the purpose of this paper to present 70 new cases of proved primary carcinoma of the gall bladder admitted to the Rhode Island Hospital from 1948 to 1958, inclusive. In addition, a review of the literature, including a cumulative analysis of cases from the last 10 years of the American literature, is presented, in order to assess possible differences, apparent or real, from earlier studies of the disease. Finally, a discussion of controversial and newer aspects of diagnosis and therapy is included with a view to reaching a rational and practical approach to this insidious malignancy.

INCIDENCE

The exact incidence of carcinoma of the gall bladder escapes definition because of a multiplicity of factors. Its relative incidence, however, has been described by many authors.

Burdette,[10] interpolating from Warren's figures on cancer illnesses, estimated that the incidence of carcinoma of the gall bladder in the general population is 2.5 per 100,000 population.

Glenn[26] and other authors quote statistics, compiled by the United States Public Health Service in 1948, which reveal that between 6,000 and 7,000 persons died of carcinoma of the gall bladder in the United States during that year.

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The incidence of carcinoma of the gall bladder in relation to all hospital admissions has ranged in recent years from 0.008 per cent in Russell's[56] group to 0.083 per cent in Donhauser's[16] series. In our own series the incidence was 70 cases in 178,204 admissions, or 0.04 per cent.

Necropsy studies in early series have been summarized by Arminski. In 206,098 autopsies, 908 cases of primary carcinoma of the gall bladder were found, an incidence of 0.43 per cent, accounting for 4.53 per cent of all carcinomas at autopsy. More recently, Goldenberg,[27] Jones,[32] and Gardner[24] found gall bladder carcinoma in 0.30 to 0.40 per cent of autopsies, and Arminski's own series of 25 cases represented 0.53 per cent of all adult autopsies.

Tragerman[67] and Arminski report gall bladder carcinoma as representing 2.1 and 2.0 per cent, respectively, of all malignancy at autopsy. While the more recent statistics do not represent significant differences with relation to autopsy incidence, Tragerman's and Arminski's compilations with regard to total malignancy are lower than any reported in Arminski's collective review which vary from 2.65 per cent (Buday[9]) to 8.10 per cent (Steinhaus[59]). This may stem from several factors—more accurate diagnosis of other biliary tract neoplasms, an increase in other malignancies, or a true decrease in gall bladder carcinoma accompanying the increasing number of cholecystectomies performed for benign disease. Which of these factors are in operation is difficult to state.

Primary carcinoma of the gall bladder occurred in 482 instances in 34,242 biliary tract operations in series reported in the United States in the past decade (Table I). This represents an incidence of 1.41 per cent and is comparable to earlier studies, though this incidence has ranged widely from below 1 per cent to 16 per cent.

TABLE I. INCIDENCE OF CARCINOMA OF THE GALL BLADDER IN BILIARY OPERATIONS

SERIES	NUMBER OF OPERATIONS	CASES OF GALL BLADDER CARCINOMA	PER CENT OF CARCINOMA
Arminski	2,500	21	0.84
Barbosa and Rate	1,055	10	0.95
Danzis	2,360	32	1.3
Donhauser	3,692	48	1.30
Fitchett et al.	1,020	29	2.8
Gardner	3,706	34	0.92
Goldenberg	1,789	30	1.7
Jesseph et al.	519	24	4.6
Jones	3,000	35	1.16
Marshall and O'Donnell	6,871	71	1.03
Rivkin	2,250	52	2.3
Roberts	2,826	44	1.56
Russell and Brown	1,488	29	1.9
Todd	666	9	1.3
Tragerman			1.89
Ulin et al.	500	14	2.8
Total	34,242	482	1.41

AGE

It is generally acknowledged that carcinoma of the gall bladder is a disease of the older age groups, the so-called "cancer age." The great majority of the patients are over 50 years of age, with most series reporting peak incidences from 55 to 70 years (Table II). The age range is wide, however;

Biering[6] in 1946 recorded a case in a girl of 13 years, the youngest case reported in the literature.

In the series at the Rhode Island Hospital, the age range was 29 to 87 years, the average age being 67.9 years. Sixty-six patients, or 94.3 per cent of our cases, were over 50 years of age. Our youngest patient, a man of 29, presented with malaise, fatigue, and chemical jaundice progressing to marked icterus, and was treated for several months for infectious hepatitis before lung metastases appeared by x-ray and the true diagnosis was established at laparotomy.

TABLE II. AGE AND SEX INCIDENCE IN CARCINOMA OF THE GALL BLADDER

AUTHOR	NUMBER OF CASES	YEARS REPORTED	AGE	WOMEN	MEN
Arminski	25	1938-47	44-77 (Average: 58.7)	23	2
Barbosa and Rate	10	—	40-82 (80% over 50)	10	0
Burdette	74	—	41-86 (Median: 67)	51	23
Danzis	32	1936-49	47-79 (Average: 60)	29	3
Donhauser	52	1935-57	—	32	20
Fish	37	—	—	—	—
Fitchett et al.	29	1936-52	— (Average: 65)	26	3
Gardner	42	1939-55	39-81 (Average: 60.7)	34	8
Glenn and Hays	56	1932-51	37-83 (Mean: 61)	41	15
Goldenberg	30	1927-51	— (97% over 55)	24	6
Jesseph et al.	24	1948-53	— (Average: 69)	14	10
Jones	50	—	— (Average: 59.1)	36	14
Marshall and O'Donnell	71	1934-56	42-81 (Average: 60.8)	54	17
McCurdy and Sawyer	12	1947-54	—	—	—
Rivkin	52	1935-55	— (Average: 59)	47	5
Roberts	45	1940-52	— (96% 50 or over)	34	11
Russell and Brown	29	1932-48	— (93% 50 or over)	23	6
Strauch	70	1948-58	29-87 (Average: 67.9)	54	16
Strohl and Diffenbaugh	59	—	—	39	20
Suma and Williams	47	1937-49	36-83 (Average: 63.7)	38	9
Todd	28	1925-55	42-77 (93% over 50)	22	6
Tragerman	173	1918-48	—	118	55
Ulin et al.	14	—	47-67 (Average: 61)	13	1
Total	1,061			762 = 75.3%	250 = 24.7%

SEX

The victims of carcinoma of the gall bladder are predominantly women. Most authors are of the opinion that this is a function of the fact that women harbor most gall bladder disease of all kinds, and this is probably a reasonable conclusion. In the collective series reviewed, 75.3 per cent of cases were women (Table II), corresponding closely to the incidence (73.1 per cent) in Arminski's study. Exceptions to this rule in several small series have been noted, however.

RACE

Carcinoma of the gall bladder is, according to most authorities, a disease of Caucasians in about two thirds of cases. Burdette and van Zandt[70] concur

in this ratio, although Boyce and McFetridge[8] are of the opinion that the disease is divided about equally between Caucasoids and Negroids. Tragerman remarks on the seemingly high incidence in Mexican women.

Our series comprised 67 white patients, 2 Negro women, and one Chinese man; however, our hospital admissions are Caucasians in all but a small percentage.

ETIOLOGY

Cholelithiasis.—The association between cholelithiasis and primary gall bladder carcinoma has been recognized by virtually every author writing on the disease. The range of incidence of gallstones in gall bladder carcinoma has ranged rather widely, however, from below 50 to 100 per cent. In the United States, since 1948, the incidence has ranged from 54.3 per cent in our study to 96.9 per cent in Danzis'[15] series (Table III).

TABLE III. INCIDENCE OF CALCULI IN CARCINOMA OF THE GALL BLADDER

SERIES	TOTAL CASES	CALCULI PRESENT	PER CENT	CALCULI ABSENT	PER CENT	GALL BLADDER NOT EXPLORED	PER CENT
Arminski	25	20	80	—	—	—	—
Barbosa and Rate	10	6	60	—	—	—	—
Burdette	74	41	55.5	11	14.9	22	29.6
Danzis	32	31	96.9	1	3.1	0	0
Donhauser	52	42	80.7	—	—	—	—
Fitchett et al.	29	18	62	2	7	9	31
Gardner	42	38	90.4	—	—	—	—
Jesseph et al.	24	15	62	—	—	—	—
Jones	50	41	82	1	2	8	16
Marshall and O'Donnell	71	42	59	4	5.6	23	35.4
Rivkin	52	41	78.8	4	7.7	7	13.5
Roberts	45	33	73	3	7	9	20
Russell and Brown	29	19	65.5	3	10.3	7	24.2
Strauch	70	37	54.3	6	8.6	26	37.1
Suma and Williams	47	35	75	—	—	—	—
Todd	28	19	68	—	—	—	—
Tragerman	173	138	79.8	—	—	—	—
Ulin et al.	14	10	71.4	1	7.1	3	21.5
Total	867	626	72				

It was of some interest to us to determine the reason for this wide discrepancy. One reason presents itself readily. This relates to the type of series described. Autopsy studies more readily determine the true incidence of stones in gall bladder carcinoma, since, no matter how extensive the disease, full dissection may be accomplished; whereas, in series comprising preponderantly operated cases, frequently only biopsy is performed, and the presence or absence of calculi in many cases is undetermined. In the collective study of 867 cases, the incidence of cholelithiasis was 72 per cent. In 349 cases, in which the contents of the gall bladder were known, however, stones were present in 90 per cent. In 10 series in which the absence of stones was recorded, the highest incidence of absence of stones was 14.9 per cent in Burdette's study.

The real controversy concerning cholelithiasis and carcinoma, however, lies not in the association, but in the relation between the two. One is easily led to the conclusion that gallstones cause carcinoma, and many have advanced this

theory in the past. In addition to the association, many authors cite the relation between bile salts, cholesterol, and known carcinogenic agents in their chemical make-up. Moreover, a good deal of experimental work in animals has been done in an attempt to prove this concept. Kazama,[34] Leitch,[42] and others before 1930 attempted, by insertion of various foreign bodies into the gall bladder, to produce carcinoma in guinea pigs and claimed to be successful. Burrows,[11] in 1933, reviewing the subject, however, denied that true neoplasia had been produced. More recently, Petrov and Krotkina[52] have again claimed the production of carcinoma in guinea pigs using intracholecystic implantation of glass tubes and radium, and Fortner[21] has produced the disease in cats by a similar introduction of methylcholanthrene pellets.

Lazarus-Barlow[39] in 1914 asserted that gallstones present in patients with carcinoma of the gall bladder produced carcinoma by virtue of radium content. This assertion failed to be substantiated in the study by Fortner and Norris[22] in 1955.

More recent authors tend to hedge on the nature of the relation between gallstones and carcinoma, though all recognize that cholecystectomy for all cases of cholelithiasis at the time of first diagnosis would probably result in a significant reduction of gall bladder carcinoma, and some use the threat of carcinoma as a major argument for removal of the so-called "silent stone" in older age groups. Pack[51] estimates that between 5 and 10 per cent of persons with cholelithiasis will eventually develop gall bladder malignancy. Glenn states, "It seems reasonable to assume that up to five per cent of the patients with gallstones who reach the age of sixty-nine . . . may develop carcinoma of the gall bladder."

Several arguments may be advanced against calculi as a causative factor in gall bladder carcinoma. First of all, the incidence of carcinoma in cases of cholelithiasis is extremely low, recent clinical series showing incidences of 0.66 per cent (Russell), 1 per cent (Burdette), 1.58 per cent (Strauch), and 2.9 per cent (Ulin[69]); Arminski reports an incidence of 4 per cent in autopsy studies. Earlier reports indicate a range in incidence from 1.14 (Erdmann[17]) to 15 per cent (Schroeder[58]), although most writers have found it to be 3 to 6 per cent. Second, some authors cite the series reported by Comfort, Gray, and Wilson[14] of 112 patients with asymptomatic gallstones followed for 10 to 25 years without development of a single case of carcinoma. Third, stones cannot explain the cases of carcinoma which develop in their absence, though some authors sidestep this issue by including infection as an etiologic agent.

Aschoff[2] and Lancereaux[38] advanced the theory that carcinoma caused gallstones. This theory has been generally discarded and has not been considered recently.

Infection.—Cholecystitis has been incriminated as an etiologic factor, but is extremely difficult to evaluate. The most obvious reasons for this difficulty are (1) the well-known tendency for carcinoma to induce an inflammatory response in the organ affected, and (2) the frequent association of cholecystitis with cholelithiasis. Most authors who consider infection as a cause of carcinoma of the gall bladder include it as one of a number of factors.

Benign Neoplasms.—Papillomas and adenomas have been variously regarded as benign or premalignant lesions in the past. Phillips[53] studied 500 cases of papilloma and found one case of adenocarcinoma. Mohardt[48] reported on 500 cases without finding carcinoma. Carcinomatous change in these lesions evidently does occur in rare cases, however. Adenomas also have been reported as showing carcinomatous change. One case in the series from the Rhode Island Hospital was a carcinoma in situ arising in an adenomatous polyp.

Exogenous Factors.—The newest and most intriguing methods of experimental production of gall bladder carcinoma to come forth suggest that exogenous substances introduced through the alimentary tract may have a bearing on development of the disease. Nelson and Woodward[50] in 1953 recorded the production of carcinoma of the gall bladder, liver, and bile ducts in 2 dogs fed o-aminoazotoluene for 2 to 5 years. Sternberg and associates[60] recently reported carcinoma of the gall bladder and biliary tree, often multicentric, in dogs following chronic feeding of large doses of an insecticide, Aramite. Carcinoma was found in 15 of 24 dogs sacrificed at 38 to 40 months. No calculi were found in the gall bladders of these dogs.

SYMPTOMS AND SIGNS

Carcinoma of the gall bladder is an asymptomatic disease in its early potentially curable stage. Symptoms in this period are caused by associated benign disease. It is only when the malignancy has spread beyond the confines of the gall bladder that it produces profound symptomatology, relentless and progressive in its natural history, which results in death within months in most cases.

Patients with gall bladder carcinoma present clinically with symptoms and signs which fall into four clinical syndromes.

The most commonly and easily diagnosed of these is indistinguishable from benign biliary tract disease. This is the most frequent presenting picture of early cases and may be superimposed in many cases on a long history of biliary symptoms. The symptoms and signs may include colicky right upper quadrant or epigastric pain with or without radiation to the back, dyspepsia with fatty food intolerance, nausea and vomiting, fever, right upper quadrant tenderness, and a tender, distended gall bladder.

The second syndrome is that with which the patient most frequently presents himself to the physician. This is the syndrome of malignant biliary tract disease. It may include any of the above symptoms and signs, but includes, in addition, those indicative of a well-established (and probably hopeless) neoplastic process. Obstructive jaundice appears, accompanied by pain of severe, steady, gnawing quality. A careful history may uncover anorexia, weakness, malaise, and weight loss of marked degree over a short interval; and physical examination frequently reveals a hard right upper quadrant mass, or, less commonly, an enlarged liver. Ascites may be present.

Occasionally, these patients may present a third picture—that of hidden malignancy, which is not easily localized. Ill-defined abdominal pain and discomfort, vague gastrointestinal symptoms, marked weight loss, weakness and fatigue, and anorexia are among the prominent components of this type.

Rarely, a patient is seen at an advanced stage in which complications arising from involvement of surrounding organs overshadows the primary process. Thus, one may be led to a diagnosis of duodenal obstruction, large bowel obstruction, or gastrointestinal hemorrhage, missing or misplacing the underlying neoplasm preoperatively.

The incidence of some of the more common symptoms and signs in patients with carcinoma of the gall bladder in the recent series we reviewed are listed in Table IV. In Arminski's collective review, the incidence of pain was 76.1 per cent; jaundice, 57.7 per cent; weight loss, 64.1 per cent; and right upper quadrant mass, 53.2 per cent. In the Rhode Island Hospital series, pain was present in 89 per cent; jaundice, in 37 per cent; weight loss, in 35 per cent; anorexia, in 56 per cent; and right upper quadrant mass in 49 per cent on admission to the hospital.

TABLE IV. COMMON SYMPTOMS AND SIGNS IN CARCINOMA OF THE GALL BLADDER

SERIES	TOTAL CASES	PAIN	JAUNDICE	WEIGHT LOSS	ANOREXIA	RIGHT UPPER QUADRANT MASS
Arminski	25	20	11	11	—	9
Barbosa and Rate	10	7	8	4	4	4
Burdette	74	61	37	35	14	40
Danzis	32	—	14	—	—	—
Fish	37	29	26	30	—	14
Fitchett et al.	29	25	15	9	—	12
Gardner	42	38	18	34	—	22
Goldenberg	30	18	17	13	—	15
Jesseph et al.	24	19	15	8	9	15
Jones	50	33	35	35	20	23
Marshall and O'Donnell	71	64	26	46	—	37
McCurdy and Sawyer	12	9	6	10	—	4
Rivkin	52	47	18	—	—	42
Roberts	45	35	21	38	—	24
Russell and Brown	29	21	16	23	16	17
Strauch	70	62	26	35	39	34
Strohl and Diffenbaugh	59	35	25	38	—	—
Suma and Williams	47	42	20	19	—	22
Tragerman	173	16	108	—	—	—
Ulin et al.	14	9	9	7	—	8
Total	925	590 = 66.1%	471 = 50.9%	395 = 59.1%	102 = 39.7%	342 = 39.9%

Duration of symptoms varies widely, depending on the presence or absence of pre-existing biliary symptoms. Arminski reports a 52 per cent incidence of past history of gall bladder disease in 387 collected cases. Gardner reports pre-existing biliary symptoms in 37 of 42 cases, or 88 per cent. Thirty-one per cent of the series presented by Fitchett[20] had a history of biliary symptoms of over 10 years' duration. Thirty-six per cent of Robert's[55] series had had symptoms for over 5 years. On the other hand, Goldenberg reports that 67 per cent of patients in his study had symptoms of less than 3 months, and Jones[32] reports a similar experience, 66 per cent of patients having had symptoms for 6 months or less. Our series showed a range in duration of symptoms of from 1 day to 4 years, the average being 3.25 months.

Malignancy in patients with pre-existing biliary symptoms, however, almost invariably produces a distinct change in symptoms quantitatively, if not qualitatively. Pain becomes more severe, more constant, and changes from colicky pain to one of a more steady, gnawing nature. Most patients will be able to pinpoint this change to within a week of its occurrence.

DIAGNOSIS

The diagnosis of carcinoma of the gall bladder is virtually impossible to establish in early cases. In the more commonly seen advanced cases, however, it should be possible to place malignancy high in one's mind on the basis of history and physical examination alone. The patient over 55, with or without a previous history of biliary disease, who presents with a short history of severe symptoms of right upper quadrant pain, jaundice, anorexia, weight loss, enlarged liver or right upper quadrant mass, or any combination of these symptoms, has hepatobiliary malignancy until proved otherwise.

Laboratory studies are of little help in this disease. Anemia may be present, but more frequently is not, its incidence ranging between 10 and 40 per cent of cases in various series. Leukocytosis may be present in cases with inflammatory complications. Jaundice is obstructive by laboratory tests. Prothrombin levels may be decreased. Serum alkaline phosphatase, if elevated in the absence of jaundice, should arouse suspicion of liver metastasis, and, according to Leevy,[40] is the most useful determination currently available in this regard.

X-ray studies in most cases are equally unrewarding. Cholecystography, in the absence of radiopaque stones, uniformly revealed nonfunction in our series, and this coincides with the experience of Campbell,[12] Lam,[37] Mattson,[46] and others. Gastrointestinal series or barium enema may show an extrinsic mass, stomach or duodenal deformities, or fistulas between gall bladder and hollow viscera in advanced cases.

Duodenal aspiration for gall bladder bile was of little value in Lam's study. Glenn was unable to diagnose malignancy by cytologic examination of duodenal aspirate in 3 patients from whom it was obtained.

Kalk[33] advocated peritoneoscopy as a diagnostic aid in this disease, but the procedure has not gained wide acceptance, although in two of Russell's cases a diagnosis was established by this method.

In recent years, needle biopsy of the liver utilizing the Vim-Silverman technique has become a well-recognized diagnostic aid in liver disease. In cases of suspected malignancy with hepatomegaly, Leevy[41] reports 93 per cent correlation between needle biopsy and autopsy findings. Since carcinoma of the gall bladder may be massively metastatic to liver, it would seem that needle biopsy might obviate the need for laparotomy in some advanced cases. Hepatomegaly occurs in nearly one-half of all cases of carcinoma of the gall bladder. Twenty-five of our cases (36 per cent) showed liver metastases at operation. Contraindications to the procedure must be considered, however, and may be present in the form of a hypoprothrombinemic bleeding tendency in patients with marked liver involvement.

An additional promising adjunct in the diagnosis of advanced cases is the recent introduction of radio-iodine tagged rose bengal,[44] which may provide more accurate diagnosis of jaundice secondary to malignancy than has been possible in the past.

In our series, a diagnosis of gall bladder carcinoma was seriously considered preoperatively in only 8 of 64 operated cases, or 13 per cent. A diagnosis of hepatobiliary or pancreatic malignancy was diagnosed preoperatively in 19 cases, or 30 per cent. With few exceptions, the remaining cases were given preoperative diagnoses of some form of benign biliary tract disease.

PATHOLOGY

Carcinoma of the gall bladder is composed of four major types. The most common is adenocarcinoma, which may be scirrhous, papillary, or mucin-producing. Adenocarcinoma comprised 85.4 per cent of 817 cases reviewed (Table V). Undifferentiated carcinomas formed the second largest group, 6.1 per cent of cases. Squamous cell carcinomas were found in 3.3 per cent of cases. These are thought to be derived from pluripotential cells, in the basal layers of gall bladder epithelium, first described by Krompecher.[35] Mixed carcinoma, or adenoacanthoma, made up 2.6 per cent of the entire series. One case of in situ carcinoma was present in a sessile adenomatous polyp in one of our cases, and has been reported by Bertrand,[5] Glenn,[25] and others in the past. One case of lymphosarcoma of the gall bladder was excluded from the Rhode Island Hospital series. Other rare tumors in the collected series were a rhabdomyosarcoma in Fitchett's study and a melanocarcinoma in Donhauser's series. Carcinoid, reticulum cell sarcoma, and fibrosarcoma have also been reported in the literature.

Although the various types have slightly different early gross appearances, the method of spread is quite similar in all cases and is principally via lymphatics and direct extension. Blood-borne metastases are uncommon in this disease, but are occasionally observed in virtually every organ of the body.

TABLE V. HISTOLOGIC TYPES IN GALL BLADDER CARCINOMA

SERIES	TOTAL CASES	ADENO-CARCI-NOMA	UNDIFFER-ENTIATED CARCI-NOMA	SQUAMOUS CELL CARCI-NOMA	MIXED OR ADENO-ACAN-THOMA
Arminski	25	25	0	0	0
Burdette	74	50	11	3	8
Donhauser*	52	36	7	5	?
Fitchett et al.†	29	28	0	0	0
Gardner	42	37	2	2	1
Goldenberg	30	28	?	?	?
Jones	50	47	0	3	0
Marshall and O'Donnell	71	40	22	?	8
Rivkin	52	43	?	4	2
Roberts	45	39	5	1	0
Russell and Brown	29	27	0	2	0
Strauch‡	70	57	3	2	2
Suma and Williams	47	46	0	1	0
Todd	28	22	?	4	?
Tragerman	173	173	0	0	0

*3 "Carcinoma"; 1 melanocarcinoma.
†1 Rhabdomyosarcoma.
‡1 "Carcinoma"; 1 carcinoma in situ; 4 unknown.

The lymphatic drainage of the gall bladder has been well established by Jones. Submucosal and subserosal channels drain through and along the organ to the cystic node in the hepatoduodenal ligament, then to the hilus of the liver, and finally to celiac nodes. Rich communications are also present between the small gall bladder channels and the subcapsular channels of the liver.

Thus, carcinoma of the gall bladder presumably progresses in most cases from the rarely discovered in situ carcinoma to invasive carcinoma with regional lymphatic and hepatic metastases and direct extension into liver, gastrohepatic and hepatoduodenal ligaments, extrahepatic bile ducts, duodenum, stomach, pancreas, omentum, and hepatic flexure and transverse colon. Intra-abdominal carcinomatosis is the final stage.

PROPHYLAXIS

Theoretically, carcinoma of the gall bladder is a preventable disease. Given that carcinoma does not arise de novo from a normal gall bladder, but is always associated with pre-existing benign disease, it is conceivable that by subjecting the entire population to Graham-Cole cholecystograms at the age of 50 years and performing cholecystectomy on all persons with diseased gall bladders, it would be possible to prevent 80 to 95 per cent of gall bladder carcinoma. This, of course, is impractical. The incidence of gallstones in this age group of the general population has been estimated in various studies, and would appear to stand at about 20 per cent.

From another viewpoint, however, prophylactic cholecystectomy is highly practical. Choelithiasis causes a great deal more death and morbidity from complications such as acute cholecystitis, pancreatitis, perforation of the gall bladder with bile peritonitis, and choledocholithiasis, than does gall bladder carcinoma alone. Mortality in elective cholecystectomy is now less than 1 per cent in most series. Mortality in forced gall bladder operations rises to about 3 per cent, and higher in older age groups with associated disease. Moreover, the so-called "silent gallstone" cannot be relied upon to remain silent. Truesdell[68] found 50 cases of "asymptomatic" gallstones in 500 laparotomies for extrabiliary disease and, on further postoperative questioning of these patients, found that only 6 could truly be considered "silent." Comfort, Gray, and Wilson[14] followed 112 patients who refused operation for asymptomatic stones and found that over a period of 10 to 20 years, 50 per cent became symptomatic and 25 per cent required operation. Similar experiences have been documented by Jaguttis[30] and Clagett.[13]

TREATMENT

To date, there is no proved effective treatment, curative or palliative, for this disease in the vast majority of cases. In the past, the only cases in which a hope for cure was entertained were those in which the lesion was an incidental finding during cholecystectomy for associated gall bladder disease, and was confined to the gall bladder.

Limited hepatic resection was then introduced and advocated by a number of authors, among them Finsterer,[18] Thorek,[65] Gray,[29] and Scheinfeld,[57] with

no significant alteration in cure rates. More recently, Glenn and Hays[26] have proposed en bloc cholecystectomy, local liver resection to include only liver parenchyma contiguous with gall bladder bed, resection of lymphatic channels and nodes draining the gall bladder, and skeletonization of the portal structures from porta hepatis to duodenum, thereby excising all tissue anterior to the common bile duct in the hepatoduodenal ligament from the liver to the pylorus. This is obviously applicable only in early cases. The most radical approach, currently, is that of hepatic lobectomy, as advocated by Pack.[23, 51]

In the majority of cases, however, the tumor is far advanced at operation, precluding any chance of cure by even radical resection.

Palliative therapy has been chiefly directed at relieving common duct obstruction by choledochostomy or at short-circuiting portions of the gastrointestinal tract. Chemotherapy, in the form of nitrogen mustard injected into the hepatic artery at operation, has been described by Todd.[66] Burdette suggests external irradiation for palliation in squamous cell carcinomas or adenoacanthomas.

In the author's series, of 64 patients undergoing surgery, 46 (72 per cent) were advanced beyond resectability at operation. Eighteen patients (28 per cent), because of localization of gross tumor, might have been candidates for radical resection by some authors' criteria. Of these latter, 10 (16 per cent) were confined to the gall bladder, 9 of the 10 undiagnosed at operation. A complete list of all operations performed is seen in Table VI. In none of the cases was radical resection performed.

TABLE VI. OPERATIONS IN 64 CASES OF GALL BLADDER CARCINOMA AT THE RHODE ISLAND HOSPITAL*

OPERATIVE PROCEDURE	NUMBER OF CASES
Laparotomy and biopsy only	27
Cholecystectomy	25
Choledochostomy	14
Cholecystostomy	7
Gastroenterostomy	3
Appendectomy	3
Drainage of abscesses (hepatic and subhepatic)	2
Choledocholithotomy	1
Gastrectomy	1
Gastrotomy	1
Duodenotomy	1
Hiatus herniorrhaphy	1
Total	86

*All but two cases biopsied.

RESULTS AND FOLLOW-UP

The results of treatment in this disease are discouraging, to understate the matter.

Operative mortality, because of the frequency of advanced disease at the time of operation, is appalling, no matter what operation is performed. In series of nonradical procedures reported in this country since 1948, Danzis, Donhauser, Rivkin,[54] and Arminski report postoperative death in over 25 per

cent of cases. The operative mortality in limited hepatic resections for less advanced disease with only localized metastasis or extension to the liver was 13.8 per cent in Scheinfeld's 36 collected cases. Four of 7 cases in Pack's[23] group of right hepatic lobectomies died in the early postoperative period.

Significant palliation has been obtained only in early cases in which tumor recurred despite "curative procedures." Only 18 2-year survivals have been reported in the United States in the past decade.

There has been no sizable series of unselected cases which reports higher than 6 per cent 5-year survival. Most series report cures in from 0 to 3 per cent of cases. In our collected series, only 11 5-year cures, one of which was a case of melanocarcinoma, have been recorded, which represent only one per cent of the total of 1,061 cases.

Follow-up was obtained in 100 per cent of the cases at the Rhode Island Hospital (Table VII). Ten patients (16 per cent) died postoperatively. Fifty-two patients (74 per cent) were dead within 6 months of diagnosis. Two patients, both of whom had carcinomas undiagnosed at the time of cholecystectomy, died of malignancy 2 years 4 months and 3 years 6 months after operation. One patient died of congestive heart failure at 89 years of age, 4 years 8 months after cholecystectomy. Four patients are living with clinically obvious or presumed disease at 4 months, 10 months, 15 months, and 2 years 5 months postoperatively. Three patients are living and clinically free of disease at 19 months, 26 months,* and 8 years 9 months postoperatively. All of these latter 3 patients had cholecystectomies, carcinoma being undiagnosed at operation. Of the 10 patients with carcinoma confined to the gall bladder at operation, 7 are dead. Five-year survival rate is 1.43 per cent.

TABLE VII. FOLLOW-UP OF 70 CASES AT RHODE ISLAND HOSPITAL (SURVIVAL FROM DIAGNOSIS)

EXPIRED		LIVING	
INTERVAL	NUMBER OF CASES	INTERVAL	NUMBER OF CASES
0- 6 months	52	0-11 months	2
7-11 months	6	12-24 months	2
12-23 months	2	24-36 months	2
24-35 months	1	Over 5 years	1
36-47 months	1		
48-59 months	1		
Total	63		7

DISCUSSION AND CONCLUSIONS

Carcinoma of the gall bladder is not a rare disease, as had once been supposed. Over 6,000 persons die of this malignancy in the United States each year. Graham[28] stated that it accounts for 8 to 10 per cent of cancer deaths in women. According to Ulin, gall bladder carcinoma is encountered in 10 per cent of biliary operations in the seventh decade of life. It stands sixth in incidence of alimentary tract neoplasms.

The incidence of carcinoma of the gall bladder has probably not changed significantly in the past 50 years. Although studies at the Mayo Clinic from 1907 to 1940 seemed to indicate a decline in its occurrence, this is not borne out

*Carcinoma in situ.

by studies of large series of collected cases. Available statistics indicate that it is encountered in about 0.01 to 0.1 per cent of hospital admissions, 0.4 per cent of all necropsies, 1.0 to 1.5 per cent of all biliary tract operations, and 4 to 5 per cent of all malignancies.

Carcinoma of the gall bladder is a disease of the "cancer age group," about 90 per cent of cases occurring in patients over 50 years of age, with a peak incidence at 55 to 70 years. Women develop the disease three times as frequently as men. This is undoubtedly related to the preponderance of women afflicted by all manner of gall bladder disease. Caucasians are affected twice as frequently as other races combined in this country. The high incidence in Mexican women remains enigmatic.

The etiology of carcinoma of the gall bladder remains obscure. Although the association of gallstones with carcinoma is apparent and exists in 90 per cent of cases, it is my opinion that gallstones alone probably do not cause carcinoma of the gall bladder. The occurrence of carcinoma in the absence of stones in 10 per cent of cases and the low incidence of carcinoma in total cases of cholelithiasis are strong arguments against this concept. I would tend to agree with authors who think in terms of multiple factors. These factors may include chronic mechanical irritation, infection, local metabolic dysfunction, bile stasis, individual host susceptibility, and exogenous factors. Gallstones do, nevertheless, provide a peculiar clue to 90 per cent of future gall bladder carcinomas, and I agree with Glenn and Pack that between 5 and 10 per cent of cases of cholelithiasis, unoperated, will probably go on to develop carcinoma.

Papillomas and adenomas, while only rarely showing carcinomatous change, constitute an indication for cholecystectomy.

The incidence of pre-existing biliary symptoms of long standing in patients with carcinoma of the gall bladder varies widely in different series, but probably occurs in one-third to one-half of patients. Curable carcinoma produces no symptoms or symptoms identical to benign biliary disease. A change in symptomatology due to carcinoma heralds incurablility and death within months in all but a small percentage of cases.

The diagnosis of curable cases of gall bladder carcinoma depends on the surgeon at the time of operation. I believe, with Burdette and Donhauser, that every gall bladder removed in patients over 50 years of age should be opened and closely examined for suspicious lesions. In the presence of such lesions, either localized thickenings or intraluminal papillary growths, frozen section should be done.

A determined effort should be made at establishing a diagnosis before operation in advanced cases. Any patient over 50 with a change in pre-existing biliary symptoms should be highly suspected of having gall bladder carcinoma, especially if history and physical examination reveal weight loss, constant pain, jaundice, right upper quadrant mass, or hepatomegaly in any combination. Elevation of serum alkaline phosphatase in the absence of jaundice is highly suspicious of hepatic metastasis. The presence of gall bladder opacification with dye on cholecystography in the presence of carcinoma of the gall bladder is so rare as to cast grave doubt on the diagnosis. Liver biopsy should

be performed in cases with hepatomegaly, as it may establish a diagnosis of advanced malignancy, avoiding exploration of hopeless cases. More recent innovations in diagnostic study await clinical evaluation at present.

In early lesions confined to the gall bladder, I advocate the type of resection described by Glenn, namely, removal of gall bladder, liver contiguous with gall bladder bed, and lymphatic-bearing tissue of the hepatoduodenal ligament from the porta hepatis to the pylorus, en bloc, as described. This seems reasonable, since the operative mortality is not prohibitive, and since we have experienced a 70 per cent failure in such lesions by cholecystectomy alone. Baker and Lawrence[3] concur in this opinion.

While an occasional case extending beyond the confines of the gall bladder may present individual circumstances justifying radical resection, such disease is generally incurable by all past experience and does not warrant radical procedures, although attempts to relieve biliary and gastrointestinal obstruction as palliative procedures are certainly in order.

If a definite diagnosis can be established clinically or by liver biopsy, operation is contraindicated unless complicating factors, such as jaundice, perforation, or intestinal obstruction are the indications. This opinion, originally expressed by Blalock[7] in 1924, has since been shared by many authors. I feel justified in this opinion because of the proved incurability, the high operative mortality, and the uniform lack of palliation in such lesions. I know of only one cure obtained by radical resection in carcinoma grossly extending beyond the gall bladder in the past 10 years, that reported by Burdette.

Palliative irradiation therapy is conceivably justifiable in a small number of selected cases of squamous cell carcinomas.

Nitrogen mustard and other chemotherapeutic agents should be used, if at all, only in long-range experimental studies, especially since recent information indicates that such therapy may enhance, rather than retard, malignancy.

I believe with Moynihan,[49] Lahey,[36] Walters,[71] and many others that cholelithiasis, in the absence of contraindications to surgery, is an indication for cholecystectomy, whether symptomatic or asymptomatic. This opinion is not held because of the threat of carcinoma, but because of the threat of all complications. Further, the older the patient, the stronger is the indication for surgical intervention.

Carcinoma of the gall bladder continues remarkably resistant to all therapy. In the absence of effective surgical treatment for all but the earliest lesions, the best hope at present for reducing the mortality from this disease lies in earlier cholecystectomy in patients with known benign gall bladder disease.

SUMMARY

1. Carcinoma of the gall bladder has been discussed in its various aspects, including a résumé of the literature on the subject.

2. A cumulative study of cases recorded in the United States since 1948 has been presented with comparison to previous studies.

3. Seventy proved cases of carcinoma of the gall bladder from the Rhode Island Hospital during the years 1948 to 1958, inclusive, have been reviewed.

4. A discussion of more recent developments relating to carcinoma of the gall bladder, and the author's opinions on some of the more controversial aspects of the disease have been presented.

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"SECOND LOOK" FOR ADRENOCORTICAL CARCINOMA

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SINCE 1949, secondary or multiple operations have been performed for selected cases of carcinoma of the stomach, colon, and rectum. The term "second look" has been used to designate these reoperations which are performed upon asymptomatic individuals, without clinical evidence of residual tumor, 6 to 9 months after the primary resection of the lymph node–positive cancer.[2, 6, 7, 8, 9]

Recently, F. John Lewis and L. F. Peltier[2] reported a patient with chondrosarcoma of the ilium, who, at the sixth re-entry was found to be free of cancer. Their experience with that case "suggests that the general principle of 'second look' cancer surgery should be tested in some cancers other than those of the alimentary tract. The type of cancer for which this procedure might prove to be useful would be that in which residual disease could be expected to grow hidden within the abdomen, pelvis, or retroperitoneal tissues. In addition to sarcomas, such as the one described, cancers of the ovary, uterus, testis, or kidney might, in selected cases, be amenable to the same surgical attack."[2]

With this in mind the following case report is presented.

CASE REPORT

J. B., a 36-year-old white Air Force pilot, was first admitted to a hospital on May 24, 1956, complaining of right upper quadrant pain.

He gave a 3 months' history of intermittent fever and chills accompanied by a cough and a tightness in the right side of the chest. He had noted a 15 pound weight loss during that period.

Physical examination was within normal limits except for palpation of a large mass which extended 10 cm. below the right costal margin.

Cholecystogram revealed displacement of the gall bladder to the left of the second lumbar vertebra. Intravenous pyelogram revealed normal renal function bilaterally with lateral and inferior displacement of the upper pole of the right kidney. All other x-ray studies were normal.

On Aug. 24, 1956, he was explored and a large, 25 by 20 cm., retroperitoneal mass, thought to be hypernephroma was found. The liver appeared grossly normal.

A right nephrectomy was performed, but the tumor had not involved the kidney. The mass was thought to be inoperable. Biopsy revealed a carcinoma of the adrenal cortex.

When fully recovered, the patient was transferred to the U. S. Naval Hospital at St. Albans.

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His condition was essentially the same, and on physical examination, a large right upper quadrant mass was felt.

Liver function studies showed an obstructive-type hepatitis. Urinary 17-ketosteroids, eosinophil count, and other laboratory studies were normal.

Chest x-ray revealed an elevated right diaphragm but no evidence of metastases.

He was re-explored on Oct. 5, 1956, through a right thoracoabdominal incision. The tumor had displaced the liver to the left and was well encapsulated except at the lower pole. The tumor was removed en toto (Fig. 1). There was no evidence of metastases although there had been extension from the lower pole of the tumor mass, presumably at the biopsy site.

Microscopic examination showed adrenocortical carcinoma (Fig. 2).

The cell block prepared from the pleural effusion collected at surgery did not reveal malignant cells.

He recovered uneventfully and postoperative studies were within normal limits. He was returned to full duty several weeks later.

On July 16, 1957, 9 months postoperatively, he was readmitted to U. S. Naval Hospital, St. Albans. He was asymptomatic. All laboratory and x-ray studies were normal.

On July 31, 1957, a "second look" was performed through the abdominal portion of the previous incision. A thoracic extension was to be made if there was tumor present abdominally.

No gross evidence of disease was found after extensive exploration.

Examination of all tissue removed (including a liver biopsy) revealed no microscopic evidence of tumor.

He was returned to full duty, to be checked at 3-month intervals.

On June 6, 1959, 3 years from the time of the original surgery, and just less than 2 years from the time of the "second look," the patient was re-admitted with a firm 4 by 4 cm. mass in the right upper quadrant which was freely movable.

All chemistries at this time were normal.

A barium enema showed anterior and medial displacement of the ascending colon. An inferior vena cavagram revealed lateral displacement and elevation of the inferior vena cava by a tumor mass. Chest x-ray, bone series, gastrointestinal series, and cholecystogram were normal.

On June 30, 1959, he was re-explored. There was tumor present in the subcutaneous tissue, muscle, and retroperitoneal area with extension across the midline. Multiple liver metastases were present.

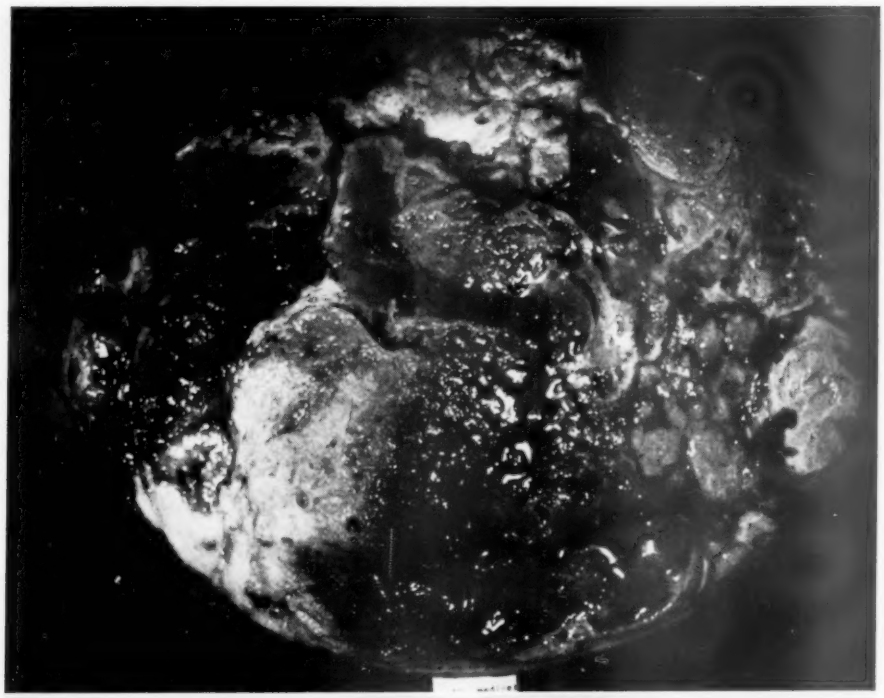
Pathology report was again adrenocortical carcinoma with a "more anaplastic pattern present, but similar to the previous tumor."

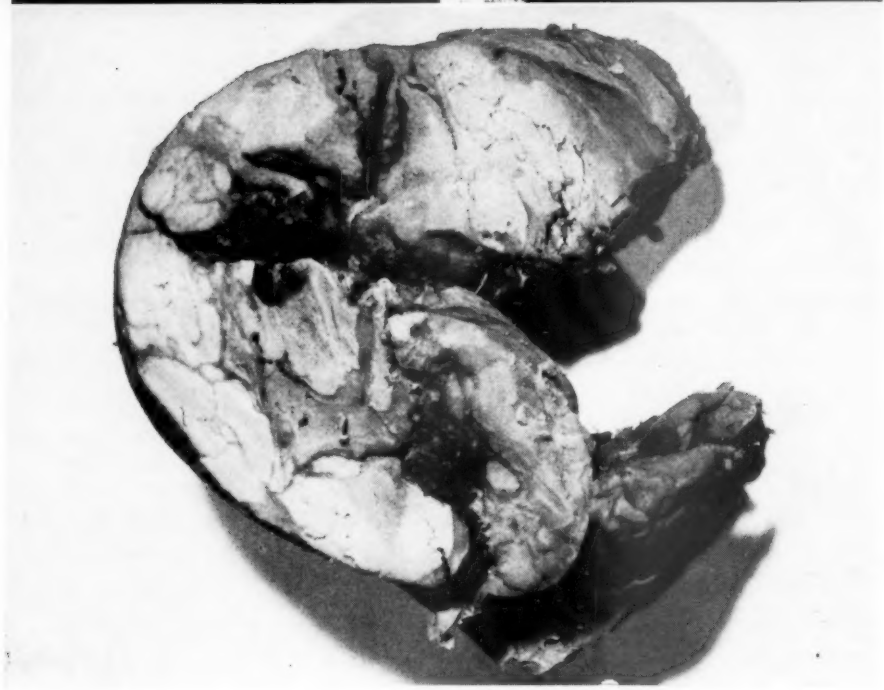
Since the tumor was nonresectable cortisone and million volt x-ray therapy was instituted consisting of 4,000 r to the right hemiabdomen through opposing anterior and posterior ports. There was some reduction in size of the tumor mass.

DISCUSSION

Dr. Wangensteen has proved that "second look" surgery has increased the survival rate in colon and rectal cancer but not in gastric cancer. Dr. Lewis has shown that it may have influenced the life expectancy in a case of chondrosarcoma of the ilium. Originally our thought of applying the "second look" principle to an adrenocortical tumor was influenced by these facts: (1) at the initial operation the tumor was not removed; (2) contamination was found from the lower pole at the definitive procedure; and (3) it has been shown by other authors that nonfunctioning adrenocortical carcinomas grow rapidly, penetrate the capsule early, and also metastasize early to the lungs, liver, brain, the other adrenal glands, and regional lymph nodes.[1, 4, 5, 10]

A.

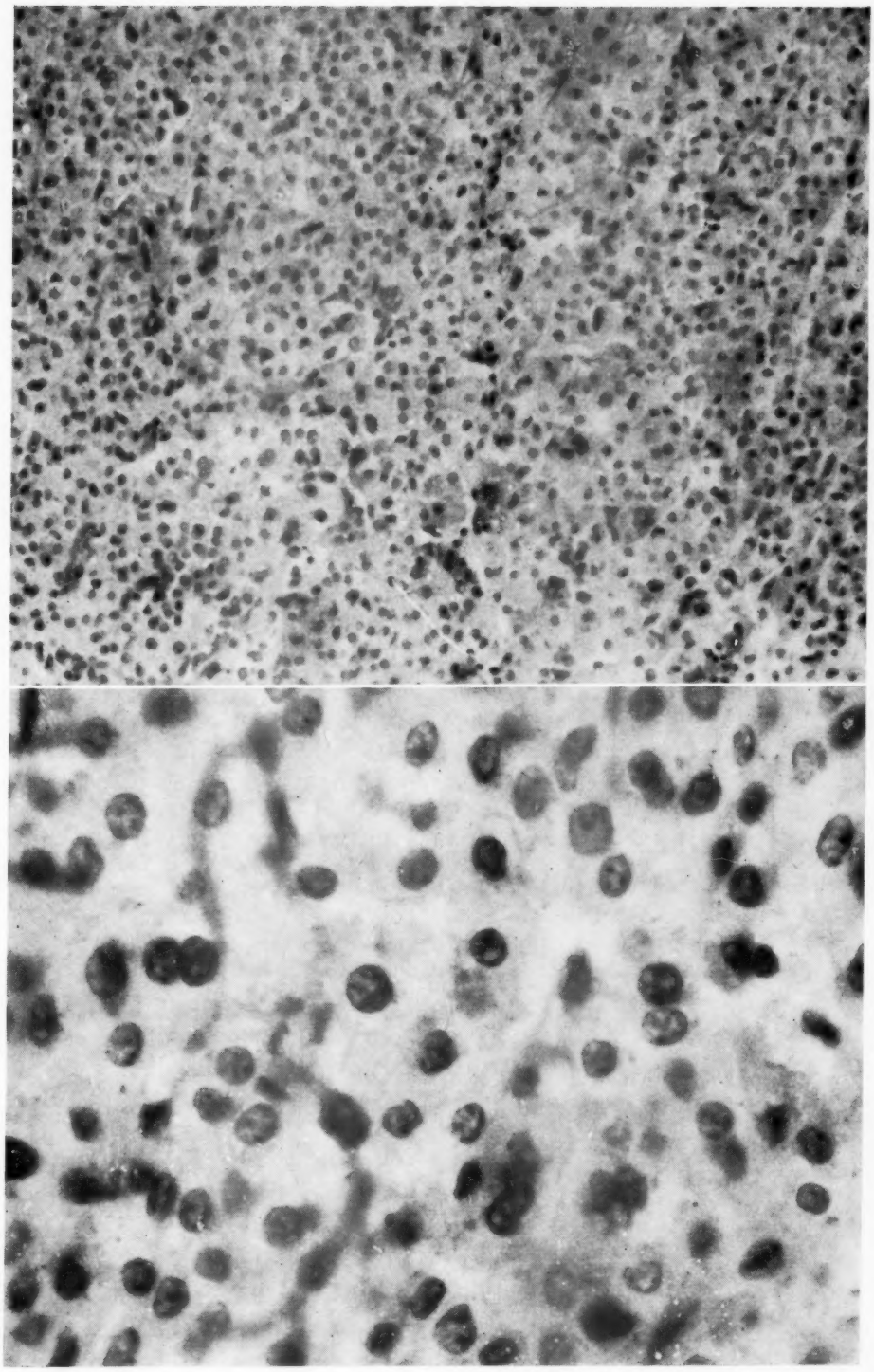




B.

Fig. 1.—*A*, Photograph of the tumor which is ovoid and smooth except at its lower pole where it is fragmented. It is encapsulated and weighs 2,547 Gm. and measures 28.5 by 15 cm. *B*, Cut section of the tumor (fixed specimen) reveals islands of bright yellow and black tissue surrounded by hemorrhage and necrosis.

A.



B.

Fig. 2.—Photomicrographs of the adrenocortical carcinoma. There are large polygonal cells with well-defined cellular margins growing in cords and separated by congested capillaries. The cytoplasm is pale, eosinophilic, and granular. The nuclei are pleomorphic and occasionally show distinct eosinophilic nucleoli. This picture is similar to that of the recurrent tumor. *A*, Low power ×200; hematoxylin and eosin. *B*, High power ×880; hematoxylin and eosin.

We chose a 9-month interval as a time for our "second look" and the patient had been followed closely up to that time. When we discovered the patient to be tumor-free at the "second look" operation and remaining so at 3-month intervals for almost 2 years we were very optimistic. And yet, 23 months from his "second look" he returned with an inoperable recurrence.

It would therefore appear that although "second looks" are beneficial in colon and rectal carcinoma it is quite difficult to assess the value of the "second look" procedure in relatively rare tumors such as adrenocortical carcinoma. We do not as yet have enough experience with these cancers to prognosticate their natural history.

This tumor apparently was of low virulence in contradistinction to other reported adrenocortical carcinomas. Yet, despite careful follow-up, when recurrence was evident, the tumor was nonresectable.

Although this isolated case is discouraging we still continue to advocate the "second look" operation in tumors of unknown virulence in addition to colon and rectal carcinomas.

SUMMARY

A case of adrenocortical carcinoma in a 36-year-old white man is described. At the initial operation the tumor was thought inoperable, but at a secondary operation the tumor was resected. There was no evidence of metastases at this time, but due to the likelihood of seeding, the patient was subjected to a "second look" operation 9 months later, at which time no evidence of tumor was present.

However, approximately 2 years after the "second look" operation the patient returned with an inoperable recurrence in the retroperitoneal tissue and liver.

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ADRENOCORTICAL FUNCTION AFTER MAJOR SURGICAL OPERATIONS AND THERMAL TRAUMA IN MAN

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DURING the last decade much evidence has accumulated demonstrating increased adrenocortical activity after trauma. The adrenal response to surgical trauma has been extensively studied; the response to thermal trauma, however, has not been as thoroughly investigated, even though burns have been considered to be one of the most intense stimuli in the provocation of the stress response in man.[3, 23] The augmented adrenocortical activity after trauma has been measured by the rapid fall of circulating eosinophils in the peripheral blood,[3, 5, 8, 18, 22] by retention of sodium and increased excretion of potassium in sweat and urine,[8, 13, 14] by increased steroid excretion in the urine,[3-6, 10, 14, 23] and by increased plasma levels of 17-hydroxycorticosteroids.[2, 6, 10, 16, 19]

The purpose of this study was twofold: (a) to measure the adrenocortical response after two different types of trauma, major surgical operations and thermal injury (variations in extent of body surface area burned furnished a convenient and objective way of demonstrating increasing gradations of stimuli for endogenous ACTH production); and (b) to determine whether the adrenocortical response is maximal in the early post-trauma period after surgical and thermal trauma by means of the administration of a standard intravenous ACTH infusion as described by Laidlaw and associates.[9]

Sandberg[16] and Steenburg[20] have administered 25 units of ACTH intravenously in the early postoperative period and noted increased plasma levels of 17-hydroxycorticosteroids over and above the levels due to surgery itself. Sandberg interpreted that finding to mean that the adrenal response to surgery was not maximal, while Steenburg thought it to mean that trauma had altered the metabolism or conjugation of 17-hydroxycorticosteroids. No similar hormonal studies have been reported in the early postburn period, although Sevitt[17] has shown that there was a normal fall in circulating eosinophils after intramuscular administration of ACTH in those burned patients with eosinophil counts sufficiently high to test.

This report presents data on the urinary excretion of 17-ketosteroids and 17-hydroxycorticosteroids in a group of 29 surgical patients and 44 burned patients. These excretory products have been determined in order to measure

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some of the known functions of the adrenal glands, even though it is well known that other tissues, such as the testes, produce hormones which are excreted as 17-ketosteroids.

In order to avoid confusion the presentation of the methods and results of each type of trauma will be given in separate sections. Part A will deal with patients after major surgical operations, and Part B will include the patients who suffered burns of more than 10 per cent of the body surface area.

PART A: SURGICAL PATIENTS

Materials and Methods.—The data herein presented were obtained in the study of 19 women between the ages of 25 and 65 years and 10 men between the ages of 26 and 75 years. All patients were residents of Lima, Peru (at sea level). The surgical operations performed on this group of individuals included: 9 subtotal gastrectomies, 10 cholecystectomies, 5 cholecystectomies with appendectomies, 1 gastrectomy and cholecystectomy, 1 jejunostomy, 1 esophageal resection, 1 sigmoidectomy, and 1 gastroenterostomy. Anesthesia with Pentothal and ether was used in all of the operations.

Each patient was studied over a period of 5 days, including one preoperative and 4 postoperative days. Accurate measurements of fluid ingested and lost during this time period were obtained. The fluid therapy administered to these patients during the postoperative period consisted of the following regimens: (1) 20 patients received 1 L. of physiologic saline daily by vein together with 1 to 3 L. of 5 per cent glucose in water by vein or 1 to 2 L. of water by mouth daily during the postoperative days; (2) 7 patients received a quantity of an isotonic saline solution* equivalent to 10 per cent of body weight by vein during the day of operation followed by half that amount of saline solution by vein during the first postoperative day, and afterward 1 to 3 L. of 5 per cent glucose in water by vein or water by mouth was given daily during the succeeding 2 days; (3) 2 patients received 1 to 4 L. of 5 per cent glucose in water by vein and/or 1 to 2 L. of water by mouth daily during the postoperative days.

On the first and second postoperative days 25 mg. of ACTH (Armour) were given intravenously in 1,000 ml. of 5 per cent glucose in water over a period of 8 hours to 9 of the women and to 6 of the men. The patients who received ACTH were strictly alternated with a group of patients who received no ACTH.

Gastric suction was practiced in all of these patients for the first or second day after surgery. Antibiotics and analgesics were given routinely. No cortisone, desoxycorticosterone acetate, or norepinephrine was used.

Urine collection: The urine was collected during each 24-hour period in bottles which were stored at 4° C. immediately after the collection period until the analyses were performed a day or two later.

Chemical methods: Aliquots of 24-hour urine volumes were analyzed in duplicate for 17-ketosteroids by the Zimmermann reaction as employed by Vestergaard[21] and 17-hydroxycorticosteroids by the Porter-Silber reaction as

*Containing 141 mEq. per liter of sodium, 1.5 mEq. per liter of calcium, 114 mEq. per liter of chloride, and 28 mEq. per liter of bicarbonate.

modified by Smith and Reddy.[19] Normal daily urinary excretion of 17-ketosteroids ranged from 6 to 24 mg. in men and from 4 to 14 mg. in women. Normal daily urinary excretion of 17-hydroxycorticosteroids in men and women varied from 1 to 11 mg.

Statistical analysis: Throughout this paper wherever a difference is said to be statistically significant or significant, this statement means that the difference has statistical significance at the 5 per cent level ($p < 0.05$) on the basis of the "t" test.

Illustration technique: Values for all patients have been combined to get an average value on the preoperative and operative days. Thereafter, the average value of each group is plotted separately. Patients who received ACTH are labeled ACTH group, while those who did not receive ACTH, control group.

Results.—None of the patients died during the time of the study or during the convalescent period. Data from all patients, regardless of sex or therapy regimen, have been combined here, since these variables showed no significant differences in average preoperative or operative day steroid excretion. It must be pointed out, however, that steroid excretion during the 2-day period of ACTH infusions was higher in male than in female patients. No complete list of daily urine volumes is given here, since daily volumes of all patients varied between 600 and 3,500 ml., quantities considered sufficient to denote adequate excretion, for the most part, of the materials measured (see Table I for average 4-day urine volume).

TABLE I. URINARY DATA IN 4-DAY POST-TRAUMA PERIOD

PARAMETER MEASURED	SURGICAL OPERATIONS (AV. ± S.E.)	BURNS	
		MODERATE (AV. ± S.E.)	EXTENSIVE (AV. ± S.E.)
Urine volume (liters/4 days)	6.0 ± 0.55	4.0 ± 0.64	2.5 ± 0.36
17-Hydroxycorticosteroid excretion (mg./4 days)	75.5 ± 12.0	68.3 ± 6.0	89.3 ± 9.6
17-Ketosteroid excretion (mg./4 days)	16.7 ± 2.7	29.5 ± 4.5	24.7 ± 3.4

17-Hydroxycorticosteroid excretion: Fig. 1 illustrates the daily excretion of 17-hydroxycorticosteroids in the urine during the time of the study.

Control group. The preoperative steroid excretion of all patients was within the normal range except for three individuals who had values higher than normal. The average value, however, was within the normal range. On the day of operation the average excretion of steroids rose 16.8 mg., a significant increase over the preoperative value. Only 3 of the 29 patients did not show a rise on the operative day: one woman who had a cholecystectomy and appendectomy and two men, one of whom had a cholecystectomy with drainage and another who had a subtotal gastrectomy. Afterward there was a gradual decline of steroid excretion in the ensuing days toward the normal range.

ACTH group. On the first day of ACTH infusion there was an additional significant average rise of 9 mg. of 17-hydroxycorticosteroids in the urine over the previous day. Eleven of the 15 patients demonstrated an increase on that day. On the second day of ACTH infusion 5 of the 15 patients showed a further increase of steroid excretion, while the remaining 10 patients demon-

strated a diminished 17-hydroxycorticosteroid excretion on that day with an average decrease of 1.7 mg. for the whole group. The 17-hydroxycorticosteroid excretion of the ACTH group, however, was significantly higher on both days of ACTH infusion compared with the control group.

17-Ketosteroid excretion: In Fig. 2 the daily urinary 17-ketosteroid excretion is plotted.

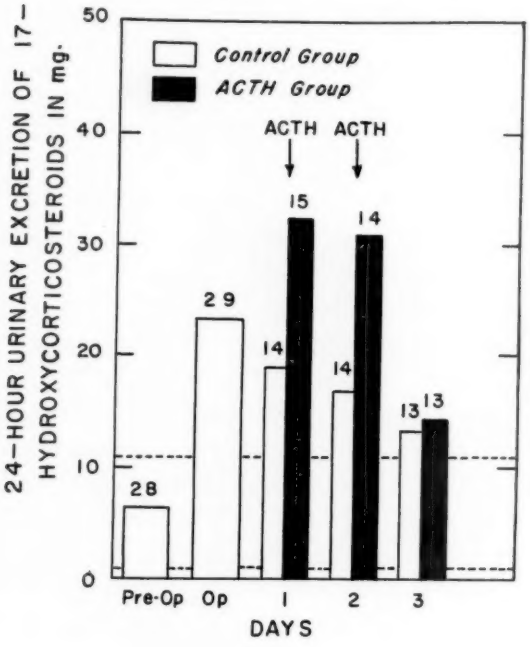

Fig. 1.

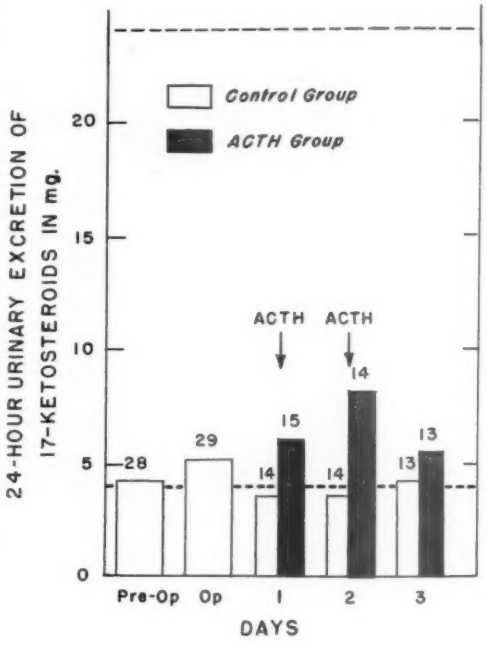

Fig. 2.

Fig. 1.—Daily urinary excretion of 17-hydroxycorticosteroids in adults after major surgery. (Key: The interrupted lines represent the range of normal values. Numbers above the bars represent the number of values used in the determination of the mean value.)

Fig. 2.—Daily urinary excretion of 17-ketosteroids in adults after major surgery. (For key, see Fig. 1.)

Control group. The preoperative steroid excretion of 17 of the 29 patients was below the range of healthy individuals, even though the average value fell into the minimal normal range. On the day of operation only 1 of the 29 patients showed an elevated excretion of 17-ketosteroids above the normal range, but 13 of 29 patients had an increased steroid excretion over the preoperative day. The average rise, however, was only 0.8 mg., a value that has no statistical significance. The majority of patients showed a diminution of steroids in the urine on the first postoperative day and were essentially unchanged thereafter.

ACTH group. Eleven of 15 patients demonstrated an increase of 17-ketosteroid excretion (but not above the normal range) on the first day of ACTH infusion compared with the previous day, but the average rise was not statistically significant over that on the day of operation. Seven of the 15 patients showed a further elevation on the second day of infusion. Average steroid excretions were 2.6 and 4.7 mg. higher in the ACTH group than in the control group on the first and second postoperative days, respectively. These differences were statistically significant.

PART B: BURNED PATIENTS

Materials and Methods.—Studies were performed on 44 burned Peruvian adults, 12 males and 32 females, varying in age from 12 to 67 years with burns involving 10 to 50 per cent of the body surface area. Analyses were made on urine collected during the first 6 days after thermal injury. Since the degree of thermal injury is related to the extent of body surface area burned, patients were divided into two groups on the basis of surface area injury: (a) 10 to 25 per cent body surface area burned (moderate burn) and (b) 26 to 50 per cent body surface area injured (extensive burn).

Because the patients studied herein were included in the burn shock study in progress in Lima, Peru,[12] the fluid therapy of this group was strictly alternated between two distinct therapy regimens during the first 48 hours after burning: (1) the saline group received an isotonic saline solution* equivalent to 10 per cent of body weight during the first day after burning and half that amount the second day, and (2) the colloid group received during the first 48 hours after thermal trauma an average quantity of plasma, blood, or polyvinyl-pyrrolidone equal to 0.6 ml. per kilogram of body weight for each percentage of body surface area burned supplemented by glucose and water to a total quantity of fluid equal to 10 per cent of body weight. On the third to seventh day after burning the only fluid or food administered to both groups of patients included 1,000 ml. of milk (25 mEq. of sodium and 40 mEq. of potassium) and 1 to 2 L. of water per day.

Twenty-five milligrams of ACTH (Armour) was given to 19 patients. The ACTH was added to 1 L. of 5 per cent glucose in water and was administered intravenously over a period of 8 hours on the third and fourth postburn days. Of the total 19 patients given ACTH, 11 had received saline therapy and 8, colloid therapy.

Of the total 25 control patients (not given ACTH), 17 had received saline therapy and 8, colloid therapy.

During the 6-day postburn period all patients were treated by the exposure method without covering any part of the body area burned, and all received 1,000,000 units of penicillin G in divided dosage daily. Again no cortisone, desoxycorticosterone acetate, or norepinephrine were administered.

The methods reported with the surgical patients are the same as were used here. Statistical significance again refers to the 5 per cent level ($p < 0.05$), and the technique of illustration is the same as before.

Results.—No deaths occurred in the group with moderate burns (10 to 25 per cent body surface area burned) during the 6-day postburn period. There were, however, 5 deaths in the group with extensive burns (26 to 50 per cent body surface area burned). Two of these were in the control group and 3 were in the ACTH group.

Data from all patients, regardless of sex or therapy regimen, have been combined, since these variables showed no significant differences in average steroid excretion on the first 2 postburn days. The daily urinary volumes of these patients varied between 200 and 3,000 ml. per day.

*Containing 140 mEq. per liter of sodium, 93 mEq. per liter of chloride, and 47 mEq. per liter of bicarbonate.

Oliguria with daily urinary volumes below 600 ml. during at least one day of the 6-day postburn period was present in some of the patients with moderate burns and in many of the patients with extensive burns. The oliguria lasted for a shorter period of time, for the most part, in patients with only moderate burns (see Table I for average 4-day urinary volume).

17-Hydroxycorticosteroid excretion (Fig. 3): Throughout the 6-day postburn period of those patients who did not receive ACTH, the average urinary steroid excretion of both moderate and extensive burn groups was elevated above the normal range. Significantly greater steroid excretion was observed in the extensive burns on the first, second, fifth, and sixth postburn days than in the group with moderate burns.

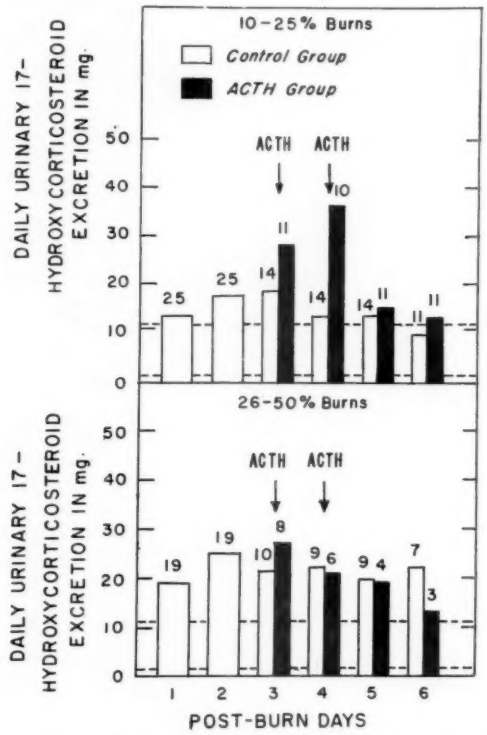

Fig. 3.—Daily urinary excretion of 17-hydroxycorticosteroids in burned adults. (For key, see Fig. 1.)

Moderate burns.

Control group. Seventeen of 25 patients demonstrated a further increase in urinary excretion of 17-hydroxycorticosteroids on the second day over the first day (4.2 mg. average rise), after which the majority of patients showed a progressive fall. The average steroid excretion diminished after the third postburn day.

ACTH group. Eight of 11 patients showed an additional rise of steroid excretion on the third day and 9 of 11 patients on the fourth day over values of the preceding day. Average steroid excretions were 9.0 and 21.9 mg. higher in the ACTH group than in the control group on the days of ACTH infusions. These differences were statistically significant.

Extensive burns.

Control group. Thirteen of 19 patients demonstrated a further increase in excretion of steroids on the second postburn day over the first (6.3 mg. average rise), after which the majority of patients showed a fall in 17-hydroxycorticosteroid excretion during the next day with only slight variations thereafter.

ACTH group. On the first day of infusion of ACTH, only 4 of 8 patients showed an additional rise of steroid excretion over the level of the preceding day, while 5 or 6 patients manifested a drop in steroid excretion on the second day of infusion. Average steroid excretions were 5.6 mg. higher on the third postburn day and 1.2 mg. lower on the fourth postburn day in the ACTH group than in the control group on days of the ACTH infusions. These differences were not statistically significant.

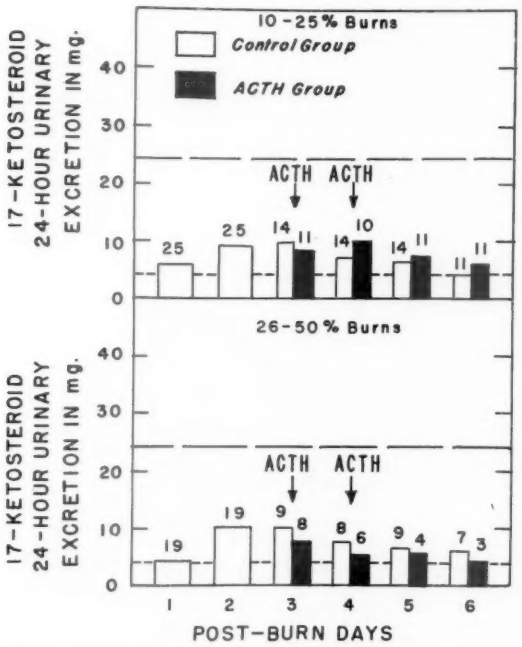
10-25% Burns
Control Group
ACTH Group
17-KETOSTEROID 24-HOUR URINARY EXCRETION IN mg.
ACTH ACTH
25 25 14 11 14 10 14 11 11
26-50% Burns
19 19 9 8 8 6 9 4 7 3
POST-BURN DAYS

Fig. 4.—Daily urinary excretion of 17-ketosteroids in burned adults. (For key, see Fig. 1.)

17-Ketosteroid excretion (Fig. 4): In general, throughout the period of study of those patients who did not receive ACTH, the urinary excretion of 17-ketosteroids was low as reflected by the average values given in Fig. 4. Only 5 patients (all female) showed values higher than normal for their sex at some time during the 6-day postburn period. The slightly higher average steroid excretion in the extensive burns compared to the moderate burns did not show statistical significance on any of the first 6 postburn days.

Moderate burns.

Control group. 17-Ketosteroid excretion was increased on the second postburn day over that of the first in 17 of 25 patients (3.4 mg. average rise). On the third postburn day only 4 of 14 patients showed additional increases (0.7 mg. average rise), after which there was a gradual average fall in the ensuing days.

ACTH group. Seven of 11 patients showed an additional rise in 17-ketosteroid excretion over the previous day after ACTH infusion, although the average value showed no rise. On the fourth day 6 of 10 patients showed an increase of steroid excretion over the previous day with an average rise of 1.8 mg. The differences in excretion between the ACTH and control groups, however, did not show statistical significance on either day of ACTH infusion.

Extensive burns.

Control group. Fifteen of 19 patients showed an increased urinary excretion of 17-ketosteroids on the second postburn day compared with the first day (5.3 mg. average rise), after which there was gradual decline of average values.

ACTH group. In 5 of 8 patients who received ACTH, there was an additional rise on the third day over the previous day, even though the average manifested a fall of 2.3 mg. On the fourth day only 2 of 6 patients showed an increase of steroid excretion over the previous day with an average fall of 2.8 mg. The lower 17-ketosteroid excretion of the ACTH group compared to the control group on the third and fourth postburn days, however, did not show statistical significance.

DISCUSSION

In this study adrenocortical function has been determined by the measurement of urinary 17-hydroxycorticosteroid and 17-ketosteroid excretion. To test whether the adrenal response was maximal under conditions of trauma, where it is believed that endogenous ACTH production is increased, the excretion of 17-hydroxycorticosteroids and 17-ketosteroids was determined during the early post-trauma period in the absence as well as in the presence of exogenous ACTH administered intravenously. The intravenous administration of a standard dose of ACTH has been shown to increase both the excretion of 17-hydroxycorticosteroids and 17-ketosteroids in normal men, with greater excretion of 17-hydroxycorticosteroids,[7, 15] and to have little or no effect upon excretion of these excretory products in patients with adrenal pathology.[7] Since it appears generally accepted that hydrocortisone (excreted as 17-hydroxycorticosteroids in the urine) is the principal hormone elaborated by the adrenal cortex on ACTH stimulation,[7, 11] it was believed that if the adrenal response were maximal after trauma, the administration of exogenous ACTH would produce no significant rise in the excretion of 17-hydroxycorticosteroids over that due to endogenous secretion alone. The same test applied in the case of 17-ketosteroid excretion, however, might be more difficult to evaluate since tissues other than the adrenal glands (such as testes) produce hormones which are excreted as 17-ketosteroids. The production of these hormones by the testes could be influenced by factors other than ACTH.

The results of this study demonstrate that 17-hydroxycorticosteroid excretion was maximal only after extensive injury due to thermal trauma, since exogenous ACTH significantly stimulated an increased 17-hydroxycorticosteroid excretion after major surgical operations and moderate thermal injury.

17-Ketosteroid excretion, however, was maximal, as judged by the ACTH test, after all grades of thermal trauma studied, whereas exogenous ACTH produced a significant rise of 17-ketosteroids after major surgical operations.

Table I compares the average steroid output obtained in the operated patients with that of the burned patients over a 4-day post-trauma period. Handling of the data in this manner would tend to minimize daily differences due to oliguria and therapy in the early post-trauma period. One report has been published demonstrating a direct correlation of 17-hydroxycorticosteroid excretion with urinary output.[1] In spite of the fact that the urinary volume was significantly lower after thermal injury compared with that after surgical operations in this study, 17-hydroxycorticosteroid excretion was, nevertheless, greater in the extensively burned patients. 17-Ketosteroid excretion was significantly increased after both moderate and extensive burns compared with that of the surgical patients. This difference cannot be ascribed to a different sex distribution between the two types of trauma; in fact, approximately 70 per cent of the patients were women in both types of trauma. Therefore, in spite of the difficulty in controlling the many variables in such a clinical experiment, it does seem reasonable to conclude that the adrenal response after extensive thermal trauma was greater than after surgical trauma incurred during major operations.

SUMMARY AND CONCLUSIONS

Daily urinary output of 17-hydroxycorticosteroids and 17-ketosteroids was studied in 29 patients who underwent major surgical operations and in 44 patients with burns of 10 to 50 per cent of body surface area. In order to test whether the adrenal cortex was stimulated maximally by the trauma itself, an intravenous infusion of 25 mg. of ACTH was administered in 1,000 ml. of glucose in water over an 8-hour period in the early postoperative and postburn periods. The ACTH infusion was given to approximately one half of the patients after surgery and to one third of the patients after thermal trauma on an alternate case basis.

The results demonstrated an elevated excretion of 17-hydroxycorticosteroids above the normal range in over 75 per cent of the patients after both types of trauma. In burned patients the average 17-hydroxycorticosteroid excretion was significantly higher in the more extensive burns. The urinary excretion of 17-ketosteroids, on the other hand, was only rarely elevated above the normal range after both types of trauma, and there was no significant direct correlation between excretion of 17-ketosteroids and severity of burn.

The application of the standard ACTH test to some of these patients produced a significant increase of 17-hydroxycorticosteroid excretion above that of the control patients after major surgical operations and after burns of 10 to 25 per cent of body surface area. In patients with 26 to 50 per cent burns, however, there was no significant increase in 17-hydroxycorticosteroid excretion after exogenous ACTH stimulation. Because hydrocortisone is the principal hormone secreted by the adrenal cortex on ACTH stimulation, these

data have been interpreted to mean that the adrenocortical response was maximal only after extensive thermal injury and not maximal after surgical trauma or moderate burns.

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EMERGENCY CECOSTOMY IN ULCERATIVE COLITIS WITH ACUTE TOXIC DILATATION

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ATTENTION has been directed in recent years to an acute, often ominous, complication which may occur in the course of nonspecific ulcerative colitis, which consists of segmental or universal dilatation of the diseased colon, with severe toxemia and signs of impending or actual perforation.

A case of fulminating chronic ulcerative colitis was reported in 1951 by Madison and Bargen,[9] which presented enormous distention of the transverse colon without distal obstruction, and signs and symptoms of perforation of the large bowel. Lumb, Protheroe, and Ramsay[7] (1955), in the course of a study of 320 cases of ulcerative colitis, noted 7 instances in which colonic dilatation was a prominent feature, in 5 of which the clinical picture was very acute. Three additional cases were reported by Lumb[5] in 1958. Pathologic study of the specimens obtained in both series revealed the presence of a severe destructive process involving all coats of the colonic wall.

Lumb and Protheroe[6] studied 152 surgical specimens of ulcerative colitis and noted that occasionally the acute inflammatory process may spread to involve the muscle coats, destruction of which may lead to perforation and sometimes dilatation. Including the 10 cases previously reported, there were 12 cases in which colonic dilatation was a striking feature of the disease. In 11 of these, the colon, when removed at operation, showed extensive thinning of the bowel in the dilated area with marked vascular congestion and widespread inflammatory infiltration causing destruction of the muscle coat. There was evidence in these specimens of acute perforation at the time of operation or chronic adhesions between the colon and the anterior abdominal wall suggesting that perforation had taken place at some earlier date. It was also noted that the dilatation was maximal in the transverse colon in each instance. In one case, there was generalized widening of the colon. There was no evidence of primary vascular disease to account for the destructive process in the colonic wall in these cases.

Bockus and his group[1, 2, 12] have used the term "toxic aganglionic megacolon" to describe the complication of extreme dilatation of a segment or of the entire diseased colon which they observed in 12 patients in a study of 125 severely ill hospitalized patients with ulcerative colitis who were treated surgically or medically. They were of the opinion that the complication was due actually to a complete absence of colonic motility and a tremendous distention of the colon with gas, and was not the result of obstruction. On the basis of

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pathologic studies in these cases, they postulated that the development of this complication may be dependent upon the rare occurrence of destruction of the ganglion plexuses in the submucosa and muscular layer of the wall of the diseased colon.

In 1959, two reports from The Mount Sinai Hospital were concerned with acute toxic dilatation of the colon in ulcerative colitis.[8, 10] One of these reports described the diagnostic features[10] of this disease complex and the other mentioned the use of cecostomy as a mode of emergency therapy.[8]

It is the purpose of this paper to present the concentrated experience at The Mount Sinai Hospital with the use of cecostomy as a primary emergency procedure in this complication of ulcerative colitis.

CLINICAL FEATURES

The clinical syndrome of acute toxic dilatation of the colon in ulcerative colitis usually appears rapidly and may occur early or very late in the course of the disease.[12]

While the dilatation is usually observed to be most marked in the transverse colon, it may be localized segmentally in the right or left portions of the large bowel. On the other hand, the colon may become universally dilated, except, as a rule, the rectosigmoid and rectal segments. Associated distention of the small bowel may also be observed, on occasion, in the roentgenograms.

In some instances, the situation may progress in fulminating fashion, with ominous prognosis. Some patients may respond favorably to conservative treatment which includes antibiotics, fluid and electrolyte replacement, steroid hormones, blood transfusions, and long tube intestinal decompression. It has also been noted[4, 10, 12] that the condition may be reversible, followed by recurrences at varying intervals.

In addition to the abdominal distention and severe toxic state, the salient features of the clinical picture include fever and leukocytosis, a silent or relatively silent abdomen, and clinical signs indicating the possibility of impending or actual perforation of the colon. The already present diarrhea may persist and perhaps increase, or the bowel movements may decrease in frequency and quantity. The fecal discharges may or may not be grossly bloody.

Actual perforation does occur in some cases, usually in the distal portion of the transverse colon or the proximal portion of the descending colon near the splenic flexure. Additional perforations have been observed in the right and left side of the colon in one case in which surgical intervention was delayed because of the patient's refusal to consent to operation.[10]

Wolf and Marshak[14] have described in detail the radiographic features noted in toxic colonic dilatation. They point out the diagnostic value of the plain or simple film of the abdomen, and note that the barium contrast enema is unnecessary and perhaps undesirable.

The clinical picture of acute, toxic dilatation of the colon may on occasion be simulated by various other conditions. The differential diagnosis must therefore include colonic perforation, peritonitis, adynamic ileus, organic colonic obstruction and, rarely, a severe grade of potassium deficiency. The latter picture has been described by Cohn, Copit, and Tumen.[4]

The serious nature of the complication under discussion is attested to by the reported morbidity and mortality encountered. In the series of 12 cases reported by Bockus and his associates,[12] one patient died among 6 who were treated medically. The other 6 patients required surgical intervention, 3 as an emergency procedure. Two of the latter died following operation. There were thus 3 deaths among the group of 12 patients.

In the series of 16 cases described in the paper by Marshak and co-authors,[10] 7 patients were treated medically. Of these, 5 improved and 2 died. Two of the 5 patients, who initially recovered from the acute episode of toxic dilatation, subsequently required ileostomy and colectomy because of recurrence of toxic dilatation. The remaining 9 patients were treated surgically, under emergency conditions, following conservative treatment for varying lengths of time. Ileostomy and subtotal colectomy, in one stage, was the procedure performed in 6 of these cases. The postoperative course was relatively smooth in one instance, complicated, stormy, and prolonged in 4, and one patient succumbed on the third day following operation. Actual perforation was found to have occurred in 4 of the latter 5 cases, including the patient who died. The perforation was sealed off, albeit by tenuous omental adhesions in one instance, and pneumoperitoneum was present in the other 3 cases.

A tube cecostomy for purposes of decompression of the dilated and distended colon was performed in the remaining 3 patients in this series who were treated surgically. In 2 of these, the clinical picture suggested the presence of a walled-off perforation in the region of the splenic flexure.

TREATMENT

The serious complications and not inconsiderable morbidity and mortality encountered in patients with acute toxic dilatation of the colon occurring in ulcerative colitis warrant an appraisal of the therapeutic measures employed. Two fundamental questions require elucidation. First, when should conservative management be discontinued in favor of surgical intervention? Second, what is the procedure of choice when operation is deemed to be necessary?

Conservative Therapy.—It is difficult to assess the relative importance of the various therapeutic modalities utilized in patients who recovered under conservative treatment. The armamentarium of present-day medical therapy includes measures directed toward the correction of fluid, electrolyte, vitamin, and hemoglobin deficits, as well as the administration of antibiotics to combat infection. The role of the adrenocortical steroid hormones is not yet clear in the therapy of this condition. Some acutely ill patients have apparently manifested marked clinical improvement under their influence. However, experience with the steroids in other cases has led to the conclusion that they may have predisposed the bowel to perforation, and perhaps retarded the localization of the resultant peritoneal inflammatory reaction.

We have the impression that long-tube intubation may on occasion have contributed to the clinical improvement observed. One such case was reported by Madison and Bargen,[9] and several by Marshak and his associates.[10]

Dilatation of small bowel loops is not infrequently seen radiographically in association with toxic dilatation of the colon. This phenomenon is thought to be due to retrograde overflow of gas and fluid through an incompetent ileocecal valve. If the paralysis of the wall of the diseased colon has not reached the state of irreversibility, the relief of intraluminal tension by drainage of this overflow may be a factor in facilitating the resumption of muscular tone.

There is no more difficult therapeutic judgment than that required when confronted with a fulminating episode in the course of ulcerative colitis, manifesting severe toxemia and increasing abdominal distention. It would certainly be desirable, if possible, to "ride out the storm" and avoid surgery during the acute period,[1] since remission may occasionally occur under conservative management. However, in these very ill patients, perforation of the colon may supervene without typical physical signs,[3] and this catastrophe may even occur during the apparent clinical improvement observed during steroid therapy. Collapse and death may also take place as the result of severe toxemia, without colonic perforation.[10]

It would seem logical, therefore, to consider surgical intervention to be urgently indicated in the event that the clinical response to medical therapy is not promptly and definitively favorable. Undue procrastination may permit the toxemia to progress to a state of irreversibility, and the destructive process in the colon to increase to a degree which leads to perforation, or at least an increase in the difficulties and hazards of the eventual surgical intervention.

Surgical Treatment.—For the most part, our experience with radical surgery (ileostomy and subtotal colectomy) in these cases has been trying both technically at operation and during the postoperative period. The difficulties are related to the fact that the bowel wall, by virtue of severely destructive ulcerations and the associated distention, becomes very thin and friable in some areas. Disruption of the bowel may readily occur during mobilization, even though the manipulation be carefully and gently attempted. Adherence of the colon in the lumbar gutters and/or to the anterior abdominal wall may also be present to add to the difficulties encountered by the surgeon. Thus, an impending or a walled-off perforation may give way, causing uncontrollable gross, fecal soiling of the peritoneal cavity and subsequent serious postoperative morbidity. In the series reported by Marshak and associates,[10] 9 patients underwent emergency surgery. The procedure in 6 of these consisted of ileostomy and subtotal colectomy. These patients developed serious complications postoperatively.

In the remaining 3 cases, the emergency surgical procedure consisted only of a tube cecostomy performed for the prime purpose of deflating and draining the dilated colon. This simple procedure was followed by prompt clinical improvement in each instance.

CASE REPORTS*

CASE 1.—E. R. (Doctors Hospital). This patient was a man, 46 years of age, who was admitted to Doctors Hospital on Oct. 26, 1946. He had had ulcerative colitis since 1941,

*Reported previously.[10, 11]

manifested by occasional periods of diarrhea, consisting of the passage of 6 to 10 daily bowel movements containing blood and mucus. The present episode of cramping abdominal pain, low-grade fever, and diarrhea had begun in September, 1946, and necessitated his admission to the hospital one month later. Previous radiographic and sigmoidoscopic examinations had found involvement of the entire colon and rectum by inflammatory changes typical of ulcerative colitis.

On admission, the patient's temperature was 100° F.; hemoglobin was 12 Gm.; white blood count was 17,750, with 82 per cent polymorphonuclear leukocytes. The abdomen was moderately distended and tympanitic. The stools were guaiac positive.

On October 28, the stools became grossly bloody, the hemoglobin fell to 8 Gm. and on the following day the patient went into shock. On conservative therapy, his condition improved over the next few days following blood transfusion therapy. On November 1, marked abdominal distention developed. The roentgenogram on the following day revealed marked distention of the entire large bowel, which was increased 2 days later (Fig. 1).

Operation was performed on November 6.* A tube cecostomy was performed in the greatly distended cecum. After gradual improvement in the patient's condition, he was discharged in December. When seen 3 months later, the patient was having but 1 to 2 bowel movements per day, and the cecostomy was practically healed.

He was well until March, 1949. He had gained 20 pounds. He was seen on March 29 complaining that during the past week he had noticed progressive abdominal distention, associated with fever, cramps, and watery diarrhea. Proctoscopy showed the rectal mucosa to be hemorrhagic, x-ray examination of the colon revealed huge distention, and the sigmoid and entire descending colon showed changes interpreted as representing small inflammatory polyps (Fig. 2).

He was readmitted to the hospital, at which time the marked abdominal distention persisted despite the continuation of diarrheal bowel movements. The scar of the previously well-healed cecostomy wound became inflamed and finally broke down with resultant fecal drainage from this site. This spontaneous cecostomy gradually resulted in reduction of the distention, the diarrhea decreased, and the patient was discharged from the hospital one month after admission.

He was last seen during the summer of 1958 and noted to be in excellent health and entirely asymptomatic.

Case 2.—E. J. (The Mount Sinai Hospital No. 80475). This 45-year-old woman was admitted to The Mount Sinai Hospital on March 26, 1957. She was first observed in April, 1952, because of the initial clinical manifestation of blood in the stools, at which time changes indicative of ulcerative colitis extending from the sigmoid to the mid-transverse colon were found. Sigmoidoscopy reported normal findings in the rectum at this time.

The present hospitalization was occasioned by the occurrence of an episode of 3 weeks of abdominal cramps, fever, diarrhea, anorexia, and weight loss. On admission, the pertinent findings were a soft abdomen, a temperature of 102.4° F., hemoglobin of 12 Gm., and a white blood count of 11,400.

On the next day marked abdominal tenderness with rebound tenderness was observed. Sigmoidoscopy to 15 cm. revealed the rectal and colonic mucosa to be injected, edematous, and friable, and erosions were seen.

Barium enema confirmed the presence of ulcerative colitis. The marked distention continued for 3 days in spite of Meticorten therapy. A simple x-ray film of the abdomen on March 31 showed marked dilatation of the transverse colon, but there was no free air in the peritoneal cavity (Fig. 3). By the evening of the following day, the patient appeared very toxic, apathetic yet restless, and the abdominal distention was extreme. Surgical intervention

*Dr. Ralph Colp.

was deemed urgently indicated. In order to avoid the operative difficulties and postoperative complications previously experienced with radical colectomy in the face of such advanced distention and dilatation, a simple cecostomy was decided upon as an emergency decompressive measure. This was readily accomplished under spinal anesthesia.

Gentle irrigation of the colon through the cecostomy tube was used postoperatively. The patient's toxicity defervesced rapidly and her general condition improved progressively. To date, the patient has remained in excellent health; she has gained over 20 pounds, and has but 1 or 2 normal or semiformed stools per day. A small purulent sinus has recurred intermittently at the cecostomy site.

CASE 3.—A. L. (The Mount Sinai Hospital No. 86978). This patient was a woman, 31 years of age, known to have had ulcerative colitis since 1952, who was admitted to The Mount Sinai Hospital on Aug. 22, 1957.

Three weeks prior to her present hospital admission, she began to have an exacerbation of colitis. On admission to the hospital, the patient's temperature was 101.4° F., and she appeared to be acutely ill. The abdomen was noted to be moderately distended, and the bowel sounds were hyperactive. No other findings were noted.

On August 26 it was noted that the abdominal distention had increased, there was tenderness to the right of the umbilicus, and bowel sounds and bowel movements had decreased. Roentgenogram of the abdomen revealed considerable distention of the colon from the rectum to the cecum. Despite steroid therapy, fever to 103° F. and bloody diarrhea continued, and on September 1 the patient was extremely ill and psychotic. X-ray examination now showed huge dilatation of the colon, most marked in the transverse segment, as well as dilatation of lesser degree of small bowel loops (Fig. 4).

The clinical picture was one of extreme toxicity, the patient appearing to be almost moribund. In view of the seriousness of the clinical condition, radical surgical intervention was considered to be inadvisable, and on September 3 an exteriorized tube cecostomy was performed under local anesthesia. The clinical response to this procedure was dramatic. Within 4 days, the temperature came down to normal and remained so during the remainder of the patient's hospital stay. She was discharged from the hospital, much improved, on October 20. After a gain of 20 pounds, she was admitted on March 5, 1958, for colectomy and ileoproctostomy. The rectum appeared normal on proctoscopic examination. She was operated upon on March 18, with a benign postoperative course.

At present, she is employed as a saleswoman, and she has but 2 to 3 well-formed bowel movements daily.

DISCUSSION

The number of cases of acute toxic dilatation of the colon treated by simple decompressing tube cecostomy as an emergency procedure is admittedly too small to permit definite conclusions regarding the applicability and efficacy of the procedure. However, the successful results obtained in the instances in which it has been employed would seem to warrant further clinical trial. It is suggested as a safe and simple means of deflating and draining the distended colon, in order to decrease toxic absorption, forestall perforation, and perhaps permit more secure walling-off of a perforation partially or tenuously sealed by fresh inflammatory adhesions.

Compared with radical extirpation of the colon, the operative trauma is minimal in an already very sick patient. Moreover, should colectomy become ultimately necessary, it may be accomplished with greater safety as an elective procedure after the patient has been tided over the acute episode.

Fig. 1.

Fig. 2.

Fig. 1.—Simple film of the abdomen showing marked distention of the ascending, transverse, and sigmoid colon, as well as moderate dilatation of several loops of small bowel. (Reproduced from Gastroenterology[11] by permission of The Williams & Wilkins Company, Baltimore.)

Fig. 2.—Barium enema examination made during the second episode of "toxic megacolon," showing huge dilatation of the colon. (Reproduced from Gastroenterology[11] by permission of The Williams & Wilkins Company, Baltimore.)

Fig. 3.

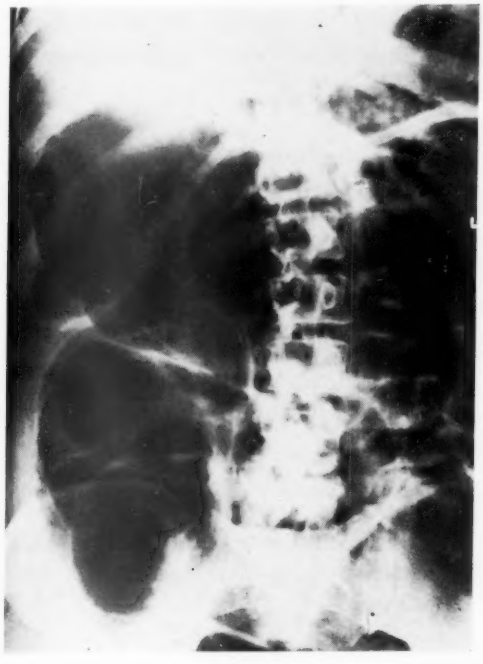

Fig. 4.

Fig. 3.—Plain film of the abdomen made 2 days after barium enema shows extreme dilatation of the transverse colon. The many small areas of retained barium indicate the presence of diffuse ulceration. There are also numerous moderately dilated loops of small bowel seen in mid-abdomen.

Fig. 4.—Simple film of the abdomen showing very marked distention of almost the entire colon, most pronounced in the transverse colon. Dilated small bowel loops are also present.

It is problematical at this time whether the procedure is applicable after actual free perforation has occurred, with resultant pneumoperitoneum and spreading peritonitis. The operative difficulties and risk notwithstanding, this critical situation requires extirpation of the perforated viscus in order to control the peritoneal infection.

In our opinion, cecostomy for decompression is preferable to ileostomy in the presence of acute toxic dilatation of the colon. Although ileostomy will accomplish diversion of the fecal stream and prevent the further addition of gas and fluid to that already trapped in the colon, it will not necessarily reduce the intraluminal colonic pressure sufficiently to forestall perforation or decrease absorptive toxemia. The wall of the colon in an advanced stage of muscular atony due to ulcerative destruction may be unable to expel accumulated gas and infected fluid, either retrograde through the ileocecal valve, even if incompetent, or forward through the distal bowel. The situation may be likened to that observed in a closed loop obstruction. The interference with the circulation of the bowel due to increased intraluminal pressure and the destruction of the bowel wall due to necrosis and ulceration are factors which lead to the danger of perforation. The loss of fluids and electrolytes into the bowel lumen, plus the toxic absorption through the denuded mucosal surface, add to the ominous clinical deterioration of the patient. Only by prompt and adequate decompression and drainage of the dilated colon can the toxic absorption be effectively alleviated and perforative complications prevented in this dangerous situation. In those patients conditioned to tolerate an extended variant of the operation, a double duty might be accomplished by adding a complemental tube or end-on ileostomy to the cecostomy.[13]

SUMMARY

1. The clinical features of "acute toxic dilatation" of the colon occurring as a fulminating complication of nonspecific ulcerative colitis are reviewed.

2. The successful employment of simple decompressing cecostomy as an emergency procedure in 3 patients presenting this ominous complication is described.

3. It is suggested that cecostomy be done without delay in patients who do not respond promptly to medical treatment, in order to forestall the development of irreversible toxemia, prevent colonic perforation, and avoid the difficulties and hazards of radical surgery performed under unfavorable clinical and pathologic conditions.

We should like to thank Drs. Bernard S. Wolf and Richard H. Marshak, of the Department of Radiology, The Mount Sinai Hospital, New York, for their assistance in x-ray interpretation.

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REPAIR OF THE LIP

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THE number of procedures described for repair of the lip after division or partial excision suggests that no method is completely satisfactory. Following the usual reconstruction there is a tendency toward notching. This is cosmetically unattractive and, if severe, predisposes to drooling. A second problem arises when a portion of the lip is excised, stemming from the fact that the width of the vermilion varies. After partial excision, unless it is the midportion, the closure will approximate segments of unequal width. It is to avoid this inequality that an Abbe-Estlander flap is swung from the contralateral rather than the ipsilateral side of the other lip. In order to overcome notching, surgeons have utilized oblique cuts, sliding flaps, overcorrection, and Z-plasty on the cutaneous or vermilion areas.

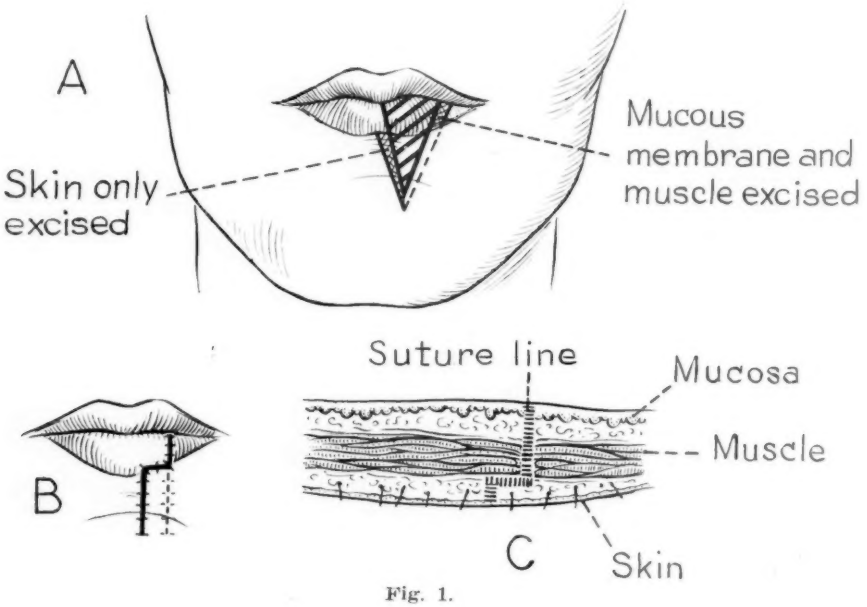

Fig. 1.

The most important step in the repair of the lip is the exact approximation of the mucocutaneous line. The second most important step is the accurate and permanent approximation of the muscle layer. The marked notching that one occasionally sees is usually the result of separation of the muscle with subsequent approximation of the suture line of the skin to the suture line of the mucous membrane.

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During the past 5 years we have utilized a type of vertical Z-plasty for repair after division or excision of a portion of the lip. A similar procedure, the halving principle, has been described by Wheeler[2] and Pickrell[1] for the eyelid. The procedure has the advantage of breaking the suture line at the mucocutaneous junction and interposing the muscle layer between the two suture lines in such a way that a marked notching should never occur.

A flap is prepared in order to overcome an abrupt change in the width of the vermilion border after excision of a portion of the lip. A strip of skin 2 mm. wide is excised from one side up to the mucocutaneous line. A 2 mm. strip of mucous membrane and muscle is excised from the other side beginning at the mucocutaneous line. When the two sides are sutured, the flaps overlap, creating a break in the suture line. The abrupt change in width of the vermilion border is tempered, with an improved cosmetic result.

We agree that meticulous closure after a straight vertical incision often produces a good result, but in a large series there are usually some that are less than desirable. The halving flap will consistently produce a good result.

SUMMARY

1. A modified vertical Z-plasty, utilizing the halving principle for division or excision of a portion of the lip, is described.

2. In our hands the cosmetic result has been superior to that obtained with other methods.

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THE RECOGNITION AND MANAGEMENT OF SEVERE HYPERTONICITY OF THE EXTRACELLULAR FLUID ASSOCIATED WITH CEREBRAL LESIONS

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SEVERE hypertonicity of the extracellular fluid has been observed in patients with cerebral lesions.[1-8, 10, 11, 14, 15, 17] Although the etiological mechanisms remain largely unknown, enough information is available to permit treatment of patients manifesting this entity in a rational manner. This discussion will indicate those situations in which severe hypertonicity of the extracellular fluid is most apt to occur and will offer a program of management that has proved efficacious in our experience.

The degree of hypertonicity of the extracellular fluid reported in patients with cerebral lesions has seldom been noted in those with other disorders. Most patients with hypernatremia and hyperchloremia, with or without azotemia, hyperglycemia, and hypokalemia, have had lesions either in the frontal lobes or the hypothalamus or both.[1, 3, 4, 7, 8, 11, 14, 17] We have observed these metabolic aberrations in a number of individuals, all of whom have had cerebral disorders. Although we have no data regarding the frequency of occurrence of this complication, we have detected it under the following circumstances: (1) after traumatic closed head injury with midbrain involvement; (2) after removal of a craniopharyngioma or a chromophobe adenoma of the pituitary gland; and (3) after rupture of an anterior cerebral artery aneurysm.

In all of the above circumstances routine postoperative determination of serum electrolytes should be obtained. Measurement of 24-hour fluid intake and urine output is also essential. In this manner the onset of this metabolic abnormality can be detected and appropriate corrective measures instituted early. There are three primary groups of patients in whom this hyperosmolal or hypertonic state has been observed: (1) in the comatose patient per se; (2) in patients with diabetes insipidus and coma, or patients with diabetes insipidus and concomitant loss of the sensation of thirst; and (3) in patients with "osmoregulatory" defects.

COMATOSE PATIENTS PER SE

We have detected 3 patients who developed hypertonicity of the extracellular fluid following external violence to the head with resultant coma. In no instance was there a previous history of either cerebral or renal disease. Usually the cerebral injury is of the closed head type. Clinical signs compatible with

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damage to the midbrain are frequent. It is usually necessary to maintain such patients on parenteral fluids for long periods of time. Most clinicians prefer to limit the quantity of fluids administered to these individuals in order to minimize the danger of producing cerebral edema.

Complete restriction of fluids in normal subjects does not result in hypertonicity of extracellular fluid. Nadal and associates[9] withheld all fluids from a normal subject for 4 days without producing significant hypertonicity of the extracellular fluid. Thirst, however, became marked; and this necessitated the administration of oral fluids.

There are several reasons why the comatose patient is more likely to develop a hyperosmolal extracellular fluid than normal persons. First, since he is unable to express the thirst of which he would complain if conscious, water deficits can progress to more advanced stages without recognition than in patients with an intact thirst mechanism. Second, patients with cerebral damage may excrete massive amounts of urinary nitrogen. Wolfman and Schoch[17] found as much as 34 Gm. of urinary nitrogen excreted in 24 hours by a comatose patient with a lesion of the midbrain. Such quantities of urinary nitrogen produce an osmolal diuresis, increasing obligatory urinary water losses. Third, some patients with midbrain damage lose control of the mechanisms regulating body temperature. Consequently, marked elevations in body temperature can also result in large losses of body water. Finally, with midbrain-damage hyperpnea, with or without polypnea, is commonly seen. Under such circumstances the quantity of water vaporized from the lungs is greatly increased. Therefore, since water requirements may be increased in comatose patients, dehydration and associated hyperosmolality of the extracellular fluid may develop rapidly if adequate quantities of water are not given.

Many comatose patients excrete large urinary volumes, frequently as high as 3,000 c.c. daily.[17] However, regardless of the volume of urine excreted, if the extracellular fluid is hypertonic, the urine specific gravity or osmolality will be high unless diabetes insipidus or chronic renal disease is present. Excretion of a large volume of highly concentrated urine does not indicate adequate body hydration but merely represents the least urinary volume in which the contained solute load can be excreted—obligatory losses.

Examination of the patient will show dryness of the mouth, tongue, and mucous membranes. In more advanced stages, hypotension may result from marked reduction in the total circulating blood volume (Table I).

Proper therapy will correct the dehydration. The quantities of fluid necessary to correct the dehydration may be determined by correlating urinary specific gravity or osmolal concentration with the amount of fluid administered. When water balance is re-established, concentrations of serum electrolytes will decrease and the urine will become more dilute. Patients who are extremely dehydrated, with associated hyperpyrexia or large obligatory urinary losses, frequently require 4,000 to 6,000 c.c. of water daily. Fluids may be given intravenously, but cerebral edema is less likely to occur if they are administered slowly into the gastrointestinal tract via a small nasogastric tube.

TABLE I. DIFFERENTIAL DIAGNOSIS OF HYPERTONIC EXTRACELLULAR FLUID

	COMATOSE PER SE		DIABETES INSIPIDUS WITH LOSS OF THIRST OR COMA		"OSMOREGULATORY" DEFECT	
	EARLY	LATE	EARLY	LATE	EARLY	LATE
24-hour urine volume	Oliguria	Increased	Increased	Increased	Normal	Oliguric to increased
Urine specific gravity	Increased	Increased	Decreased	Decreased	Decreased to normal	May be increased
Urine osmolality	Increased	Increased	Decreased	Decreased	Decreased to normal	May be increased
Urinary NaCl	Normal to increased	Decreased to absent	Normal	Normal	Decreased to normal	Normal to increased
Dry mouth and membranes	Present	Severe	Present	Severe	Absent	Minimal
Blood pressure	Normal	Hypotension	Normal to mild hypertension	Shock	Normal	Normal
Proper treatment	Water	Water	Water and Pitressin	Water and Pitressin	Water	Water

The ideal fluid for replacement not only supplies adequate quantities of water but also contains enough calories to minimize endogenous protein catabolism, thus reducing the associated osmolal diuresis. For this reason intravenous solutions of 10 per cent glucose or 15 per cent emulsified fat or both serve admirably. If replacement therapy is to be given by way of the intestinal tract, a formula of milk, carbohydrate, and an oral fat emulsion is satisfactory. As the accumulated water deficit is being corrected, replacement of electrolytes may also be required since in the early stages of water depletion electrolytes have been excreted by the kidneys in a compensatory attempt to maintain isotonicity of the extracellular fluid.[12] Later, even though the extracellular fluid is hypertonic, the total body quantities of sodium and chloride are reduced. The quantity of electrolytes which must be replaced can be estimated by determining the serum electrolyte concentrations and correlating these values with the urinary excretion of the same ions; a persistently positive sodium or chloride balance occurring while the serum levels of these electrolytes are decreasing indicates the need for larger quantities to be administered.

Interestingly, the clinical condition of patients who have been presumed to have hopeless cerebral damage frequently improves with correction of the dehydration and return of the concentrations of the extracellular electrolytes to normal.

PATIENTS WITH DIABETES INSIPIDUS AND LOSS OF THE SENSATION OF THIRST OR ASSOCIATED COMA

Patients with diabetes insipidus excrete large urinary volumes of low specific gravity or osmolality. These individuals usually do not become dehydrated because the thirst mechanism, actuated by intracellular and extracellular fluid losses, serves as a compensatory device.[13] However, if because of cerebral injury,

the sensation of thirst is not present or the patient is comatose and unable to express thirst, dehydration may occur within 24 to 48 hours unless an adequate amount of exogenous water is supplied. If the necessary supplies of water are lacking, the extracellular fluid becomes concentrated; severe hypertonicity develops more rapidly in this type of patient than in the comatose patient per se who is still able to concentrate urine.

These patients excrete large urinary volumes of low specific gravity or osmolality. Usually the osmolality of the urine is less than that of the serum. Examination of the mouth shows dryness of the mucous membranes. If the patient is conscious, dysphagia may be present. A 2 to 5 pound loss of body weight may occur in a 24-hour period of time. Occasionally, increasing lethargy or coma in a previously conscious patient results from hypertonicity of the extracellular fluid. Later, sudden circulatory collapse and profound shock may follow a gradual but marked decrease in the total circulating blood volume. Unless appropriate therapeutic measures are immediately undertaken, most of these patients die in "irreversible shock."

Appropriate management of these cases is contingent upon early recognition of this abnormality and correction of the fluid deficits. Since there is insufficient antidiuretic hormonal activity, administration of Pitressin will prevent the large losses of body fluid which might otherwise occur. Pitressin may be given either intramuscularly or intravenously. The most commonly used preparation is Pitressin tannate in oil which is administered intramuscularly. The amount of this drug required and frequency with which it is administered varies with each patient. It must be given cautiously, and the patient's response carefully evaluated. The average duration of action of Pitressin tannate in oil is 48 hours. If the patient is highly sensitive to Pitressin, or if it is given too frequently or in excessive amounts, water intoxication may occur. Fluids must be given cautiously after Pitressin therapy has been instituted, and the specific gravity, or osmolality, and volume of the urine should be determined daily. If the urinary specific gravity rises and then returns to low levels, more Pitressin must be given. Contrariwise, if oliguria occurs, fluid administration should be limited so that excessive retention of fluid and subsequent water intoxication do not occur.

In the later stages of dehydration, if shock occurs, fluids must be given rapidly to restore the circulating blood volume. If the administered fluids are to be retained, then Pitressin should also be given. Under these circumstances intravenous aqueous Pitressin is preferred, since its action is immediate and of short duration, and cumulation of the drug will not occur. If Pitressin tannate in oil is administered to a hypotensive patient, absorption occurs slowly and usually only after large quantities of fluid have been given. Consequently, significant water retention may occur 24 or 48 hours later and cause water intoxication. Once hypotension has been corrected and the extracellular fluid volume restored, periodic intramuscular Pitressin tannate in oil serves well for maintenance.

The type and quantity of solutions to be replaced are similar to those recommended for the comatose patient per se. If the patient is conscious, oral administration is preferred. If the patient is comatose, replacement may be given enterally via a nasogastric tube of small caliber. If more than 4,000 or 5,000 c.c. of fluid must be administered daily, the intravenous route should also be used to prevent troublesome diarrhea. By titrating the dosages of Pitressin with the volumes of fluid given, it is possible to correct the deficits of body fluid. When this is done and proper amounts of Pitressin are given for maintenance, the patient should excrete a 24-hour urinary volume of 1,000 to 1,500 c.c.; this urine should have a specific gravity of approximately 1.010 to 1.015.

PATIENTS WITH "OSMOREGULATORY" DEFECTS

Although there is no conclusive evidence to indicate the presence of osmoreceptors in the human diencephalon, Verney[16] has presented indirect evidence which favors the presence of osmoreceptors in that portion of the dog brain supplied by the internal carotid arteries. If osmoreceptors do exist in human beings, they should respond to small deviations in the concentration of the extracellular electrolytes. Presumably, increases in the tonicity of the extracellular fluid may normally be prevented by an "osmoregulatory" response to small increases in the concentration of the extracellular electrolytes. This response may be manifested by either an increased renal excretion of sodium and chloride ions or an inhibition of urine flow or both. If a defect in "osmoregulatory" function exists, then relatively small deficits of body water could cause hypertonicity of the extracellular fluid, since compensatory urinary losses of sodium and chloride would not occur or because antidiuresis does not result. It is possible then that the severe hypertonicity of the extracellular fluid which is observed in certain patients with cerebral damage is related to a disturbance of some "osmoregulatory" system which is operative in individuals without cerebral disorders. Such a thesis would explain those cases of extreme extracellular fluid hypertonicity occurring in the absence of clinical signs of dehydration.[3] We have studied one such patient intensively.

The development of hyperosmolality of the extracellular fluid in association with an inadequate supply of water may occur even more rapidly in individuals with these postulated "osmoregulatory" defects than in persons in the other two groups. Since minor deficits of water remain uncompensated, hypernatremia or hyperchloremia or both may develop within 48 hours after injury or operation.

"Osmoregulatory" defects should be suspected in patients who fail to regain consciousness after a head injury or cerebral operation, even though other more common causes exist. The diagnosis can be made by determining the serum electrolyte values and correlating them with urinary concentration. A low urinary osmolality or specific gravity associated with hypertonicity of the extracellular fluid is highly suggestive. For reasons yet unexplained, hyperchloremia usually precedes the hypernatremia. In the early stages of development of this pattern urinary volumes appear adequate, usually ranging from

1,000 to 1,500 c.c. daily; urinary specific gravity is low. Later, after the serum becomes more hypertonic, the urine becomes more concentrated; it is not uncommon to find the specific gravity to be 1.020 to 1.035 or the osmolality to exceed 1,200 mOsm. per liter. In some instances it appears that "osmoregulatory" response to moderate changes in serum osmolality is impaired; but when osmolal changes in the serum become great enough, some compensatory response occurs.

Treatment is aimed at correcting the fluid deficits and establishing a positive water balance. The amount of fluid required varies, but we have found that approximately 3,000 c.c. daily is sufficient if adequate amounts of carbohydrate and fat are given to lessen endogenous catabolism of nitrogen and subsequent osmolal diuresis. The fluids may be given either orally as a liquid formula or intravenously in the form of 10 per cent glucose or invert sugar and Lipomul. Again, serum electrolyte levels and urinary concentration serve as a guide to the quantity of fluid required. Once water balance has been established, a progressive fall in the serum electrolyte and urinary concentrations will be noted. To avoid cerebral edema one should attempt to lower the serum electrolyte concentrations gradually over an interval of several days rather than attempting to correct the entire water deficit in a 24-hour period. Concomitant with a return of the serum electrolytes to normal values, improvement in the patient's clinical condition usually occurs.

SUMMARY

Severe hypertonicity of the extracellular fluid may be observed in: (1) a comatose patient per se, (2) a patient with diabetes insipidus and loss of sensation of thirst or associated coma, or (3) a patient with a defect in the "osmoregulatory" mechanism.

The clinical and laboratory features of each entity and appropriate therapeutic measures are discussed.

In many instances the metabolic abnormalities may be of a temporary nature. If fluid and electrolyte homeostasis can be maintained during the acute phase, subsequent complications may be prevented.

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THE DISTRIBUTION OF RADIOACTIVE ASCORBIC ACID IN WOUNDED NORMAL AND SCORBUTIC GUINEA PIGS

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THE FACT that a substance, later identified as Vitamin C, is necessary for the normal healing of a wound has been known for centuries. According to Bourne,[1] the first clinical description of scurvy was recorded about 1500 B.C., the first autopsy studies made in 1535, first experimentally produced in 1907, and the first major pathologic study appeared in 1919. In spite of this long history and the numerous experimental studies, the exact role of ascorbic acid in wound healing has not been determined.

In our first studies of ascorbic acid, we have attempted to determine if ascorbic acid is preferentially localized in the wounds of experimental animals and to find the smallest amount of injected ascorbate which produces detectable differences in the wounds. Previously, we found that ascorbic acid accumulated in wound tissue to a greater extent than in the adjacent uninjured muscle of normal guinea pigs.[3] The organs of scorbutic guinea pigs rapidly took up intramuscularly administered ascorbic acid, but doses of 2 mg. or more of ascorbate were necessary before our analytical methods could detect an increased tissue content within the experimental period (72 hours). The use of C^{14}-labeled ascorbic acid has enabled us to study the uptake of ascorbate in numerous tissues after the administration of a single small dose of the vitamin.

METHODS AND MATERIALS

Guinea pigs weighing 250 to 350 Gm. were divided into two groups. The normal controls were fed, ad libitum, a diet consisting of rabbit pellets (Purina). The diet was supplemented daily with a multivitamin mixture containing about 25 mg. of ascorbic acid.* A muscle-splitting right rectus incision was made from the costal margin to the symphysis pubis and the wound carefully sutured with interrupted 4-0 silk through the anterior sheath, rectus muscle, and peritoneum. The skin was separately closed. Seven days postoperatively, these animals received a single dose of ascorbic acid—1-C^{14} intramuscularly. A heart puncture was made and the animals sacrificed by exsanguination at 0.5, 2 or 4 hours, and at 1, 3, 5, or 7 days after the injection.

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TABLE I. DISTRIBUTION OF ASCORBIC ACID—1-C^{14} IN GUINEA PIG TISSUES

	NORMAL GUINEA PIG AND TIME*					SCORBUTIC GUINEA PIG AND TIME*					
TISSUE	N(1) 0.5 HR. (%/GM.)†	N(1) 4 HR. (%/GM.)	N(1) 1 DA. (%/GM.)	N(1) 3 DA. (%/GM.)	N(1) 5 DA. (%/GM.)	N(1) 7 DA. (%/GM.)	S(3) 0.5 HR. (%/GM.)	S(2) 2 HR. (%/GM.)	S(3) 4 HR. (%/GM.)	S(4) 1 DA. (%/GM.)	S(3) 3 DA. (%/GM.)	S(3) 5 DA. (%/GM.)	S(3) 7 DA. (%/GM.)
Pituitary	0.13	0.17	0.19	1.09	—	0.70	0.070	—	0.54	0.36	0.49	0.13	0.018
Adrenal	2.09	1.51	3.55	0.083	0.62	0.88	0.92	1.97	1.89	1.64	2.62	0.47	0.39
Thyroid	1.52	1.12	0.14	0.033	0.31	0.67	0.93	2.32	0.94	0.83	2.59	0.28	0.23
Gonad	0.82	0.25	0.46	0.46	—	0.14	0.31	0.20	0.078	0.17	0.42	0.098	0.12
Pancreas	0.31	0.21	0.78	0.20	0.15	0.083	0.54	0.42	0.63	0.35	0.62	0.031	0.042
Liver	2.19	0.30	0.54	0.12	0.095	0.036	0.63	0.40	0.34	0.28	0.14	0.052	0.024
Spleen	0.77	0.61	1.23	0.047	0.080	0.11	0.18	0.97	0.95	0.73	1.98	0.21	0.17
Kidney	0.48	0.31	0.26	0.70	0.047	0.056	0.35	0.52	0.30	0.16	0.16	0.031	0.019
Heart	0.15	0.006	0.18	0.098	0.059	0.050	0.13	0.27	0.21	0.13	0.12	0.013	0.016
Rectus	0.13	0.039	0.033	0.038	0.027	0.016	0.13	0.077	0.043	0.16	0.14	0.005	0.013
Rectus wound	0.23	0.30	0.57	0.15	0.83	0.071	0.52	0.40	0.40	0.22	0.31	0.061	0.029
Stomach	0.56	0.31	0.51	0.13	0.092	0.086	0.26	0.21	0.33	0.21	0.19	0.039	0.024
Brain	0.041	0.041	0.18	0.16	0.14	0.15	0.010	0.040	0.033	0.078	0.079	0.046	0.042
Lung	0.78	0.14	0.78	0.27	0.14	0.14	0.34	0.94	1.03	0.42	0.44	0.14	0.081
Cartilage	0.22	0.16	0.010	0.46	0.033	0.20	0.11	0.29	0.18	0.11	0.27	0.077	0.027
Blood	0.14	0.033	0.027	—	0.007	0.009	0.077	0.041	0.025	0.012	0.030	0.004	0.003

*Time is the period after injecting ascorbic acid-1-C^{14}. The number in parentheses is the number of animals used.
†Values are recorded as percentage of administered dose per gram of tissue (wet weight).

The organs were excised, weighed, and assayed for C^{14} content. Wound tissue was obtained by excising the tissue within the sutures throughout the length of the incision.

The second group of animals was maintained on an ascorbate deficient diet[4] supplemented with a similar multivitamin mixture containing all necessary vitamins except ascorbic acid. These scorbutic guinea pigs were operated on as first described 14 days after being put on the deficient diet. Radioactive ascorbate was given intramuscularly on the seventh postoperative day and the animals sacrificed as described for the normals.

The ascorbic acid—1-C^{14} (obtained from Volk Radiochemical Company) had a specific activity of 3.38 μc per milligram. The tissues were weighed and oxidized with Van Slyke-Folch combustion fluid.[5] The carbon dioxide was collected and its activity counted in an ionization chamber. The activity was corrected for background radiation. Organs which could not be analzyed immediately were stored frozen.

RESULTS

The amounts of radioactivity of the different organs of normal and scorbutic guinea pigs sacrificed at different intervals are recorded in Table I. The values are recorded as percentage of administered dose per gram of tissue (wet weight). The labeled ascorbic acid was rapidly taken up, although in small quantities. The glandular tissues appeared to concentrate ascorbate to a larger extent than other tissues. There was no well-defined difference in the pattern of distribution in scorbutic guinea pigs as compared with the normals. Burns and his associates[2] have also reported no difference in the distribution of ascorbic acid in normal and scorbutic guinea pigs. Consistent with our nonradioactive ascorbate studies,[3] the muscle wound tissue took up more ascorbate than the adjacent intact muscle. The significance of these findings is being investigated further.

SUMMARY

Ascorbic acid-1-C^{14} was administered to normal and scorbutic guinea pigs one week after a right rectus incision had been made. The C^{14} taken up by various organs was measured at different intervals after injection of the labeled compound. The pattern of distribution of the ascorbate was similar in both the normal and the scorbutic animals. Wound tissue concentrated ascorbic acid to a greater extent than the uninjured tissue.

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THE EFFECTS OF PLASMA FROM PATIENTS WITH AND WITHOUT CANCER UPON HEPATIC REGENERATION IN RATS

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THE ability of rat liver tissue to regenerate following partial hepatectomy has been documented by Brues, Drury, and Brues,[1] Christensen and Jacobsen,[3] Higgins and Andersen,[6] and Smythe and Moore.[9] Brues and co-workers[1, 2] demonstrated that, during the first 24 hours following partial hepatectomy, there is practically no increase in the number of hepatic cells, but during the interval from 24 to 72 hours after operation the number of hepatic cells increases from 33.5 to 65.5 per cent of the number of cells originally present. Jaffee[7] states that the rate of cell division and restoration in regenerating liver is comparable to the rate of cell division of most tumors. Brues and associates[1, 2] also showed that the mass of the residual liver fragment increases 50 per cent in the first 24 hours after operation, while Higgins and Andersen[6] reported 71 per cent restoration of liver mass, 72 hours after partial hepatectomy.

The inhibition of mitosis in regenerating liver by normal rat serum has been reported by Stich and Florian,[10] while Smythe and Moore[9] obtained an inhibition of regeneration of liver mass by periodic intravenous injection of normal rat plasma. When these investigators[9] infused plasma collected from recently partially hepatectomized rats, which harbored a site of increased mitosis, into other rats similarly hepatectomized, there was an increase in the expected growth of the residual liver.

Several theories have been proposed to explain these phenomena of inhibition by normal serum and either no effect upon, or an increase in liver mass, by posthepatectomy serum. Glinos[4] believes there is an inverse relationship between the concentration of certain serum constituents and liver growth, and postulated that a decreased albumin concentration might be associated with an increased rate of liver cell division. Stich and Florian[10] suggested that in the serum of adult rats one or more factors are present which inhibit cell division in hepatic tissue and following hepatectomy these substances are diminished. Christensen and Jacobsen[3] believe that a circulating cell-stimulating substance may be present following partial hepatectomy accounting for the rate of liver restoration.

The following study was undertaken in order to explore some of the factors that might be concerned with the inhibition of regeneration of liver mass, and

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in an effort to see if there was any difference in the effect of plasma from patients without cancer, that is, those not harboring a site of accelerated mitosis, and those with cancer, that is, harboring a site of accelerated mitosis.

METHOD

This study was designed to determine the effect of the periodic intraperitoneal injection of several substances upon hepatic regeneration in the rat after partial hepatectomy. The materials injected include: pooled normal rat plasma, demineralized water, isotonic salt solution, a plasma expander, pooled normal bovine plasma, pooled normal human plasma, plasma from patients without cancer, plasma from patients with cancer, pooled plasma from patients without cancer, and pooled plasma from patients with cancer.

The white rats used in this study were from a uniform strain,* between 14 and 18 weeks of age, with a weight range of 159 to 250 Gm. The animals were maintained in air-conditioned quarters at a temperature of 70° F., plus or minus 2 degrees. There was no restriction of diet, all animals were allowed Purina Laboratory Chow and water ad libitum. All weights were determined by a triple beam balance scale.

Ether anesthesia was used at all times. All partial hepatectomies were performed and all animals were sacrificed at the same time of day, so that the diurnal variations in mitotic activity demonstrated by Jaffee[7] were constant for all animals. The partial hepatectomies were performed according to the method of Higgins and Andersen.[6] An average of 67 per cent of the total liver mass was excised (Table I). All animals survived and were sacrificed 72 hours after the procedure.

TABLE I. RELATION OF WEIGHT OF EXCISED LOBES TO TOTAL WEIGHT OF LIVER

GROUP I (20 RATS)	AVERAGE	RANGE
Total body weight	219	180-247
Weight of excised liver	4.3	3.5-5.0
Weight of residual liver	2.1	1.5-2.5
Total liver weight	6.4	4.8-7.4
Total liver weight / Weight of excised liver	1.49	1.45-1.55 SD 0.028
Per cent of liver removed	67	65-69

Brues, Drury, and Brues[1] have shown a constant ratio between the total weight of the liver and the excised hepatic tissue. The most accurate estimate of the calculated liver mass for each animal is obtained by multiplying the weight of the excised hepatic tissue by a specific factor. The factor used for this series was 1.49 (Table I). The calculated residual weight of the liver is the calculated total liver weight less the weight of the excised portion.

Several ways of expressing changes in liver weight after partial hepatectomy as a measure of regeneration have been suggested. The per cent replacement of the resected portion seems to be the most understandable and will be used here.

*Sprague-Dawley strain supplied by Bark-Bridge Farms, Wenonah, N. J.

For example, 50 per cent regeneration has taken place when the residual liver tissue has increased until one-half of the excised tissue has been replaced.

The anticoagulant for all types of blood was sodium heparin, the minimal amount to prevent clotting being used in each instance. Normal rat blood was obtained from the abdominal aorta of donor animals. The bovine and human blood was of venous origin. The isotonic salt solution was 0.9 per cent sodium chloride, the demineralized water was distilled twice and then passed over anion-cation exchange resins, and the plasma expander was Plasmoid. All materials were injected through the anterior abdominal wall. The first injection was given at the time of partial hepatectomy. Subsequent injections were given at 8-hour intervals.

OUTLINE OF THE EXPERIMENT

The median and left lateral lobes of the liver of the rats were removed through a midline abdominal incision. The rats were sacrificed 72 hours later, except those in Group I which were exsanguinated immediately after the partial hepatectomy.

Group I (20 animals).—The excised hepatic tissue was drained of blood and weighed. The animals were exsanguinated and the remaining hepatic tissue was removed and weighed. The average weight of the median and left lateral lobes and the average ratio between the total liver weight and the weight of the excised tissue was computed from these figures (Table I).

Group II (10 animals).—This control group received no treatment.

Group III (10 animals).—One milliliter of pooled normal rat plasma was injected every 8 hours.

Group IV (10 animals).—One milliliter of demineralized water was injected every 8 hours.

Group V (10 animals).—One milliliter of isotonic salt solution was injected every 8 hours.

Group VI (10 animals).—One milliliter of pooled plasma expander was injected every 8 hours.

Group VII (10 animals).—One milliliter of pooled normal bovine plasma was injected every 8 hours.

Group VIII (10 animals).—One milliliter of pooled normal human plasma was injected every 8 hours.

Group IX (15 animals).—This group was divided into five equal subgroups. Each subgroup received periodic injections of 1 ml. of plasma from a patient without cancer.

Group X (30 animals).—This group was divided into 10 equal subgroups. Each subgroup received periodic injections of 1 ml. of plasma from a patient with cancer.

Group XI (5 animals).—Two milliliters of pooled plasma from patients without cancer was injected every 8 hours.

Group XII (10 animals).—Two milliliters of pooled plasma from patients with cancer was injected every 8 hours.

The pooled plasma used for Groups XI and XII was obtained from the hospitalized patients studied in Groups IX and X, respectively.

RESULTS

Group I.—An average of 67 per cent of the liver mass was removed by partial hepatectomy (Table I). This is quite similar to the 70 per cent partial hepatectomy described by Higgins and Andersen.[6]

Group II.—After 72 hours, regeneration of the excised liver mass in the control group averaged 79 per cent, with a standard deviation of 6.7 (Table II).

TABLE II. CONTROL HEPATIC REGENERATION IN 24 HOURS

GROUP II (10 RATS)	AVERAGE	RANGE
Total body weight	205	183-220
Weight of excised liver	4.7	4.2-5.4
Calculated weight of residual liver	2.3	2.1-2.5
Calculated weight of total liver	7.0	6.3-8.0
Weight of liver after 72 hours	6.0	5.2-7.0
Calculated weight of liver regenerated	3.7	3.1-4.5
Calculated per cent of hepatic regenerated	79	71-90
		SD 6.7

Group III.—The effective inhibition of hepatic regeneration of pooled normal rat plasma is demonstrated by these animals. Regeneration in this group was 51 per cent with a standard deviation of 7.2 (Table III).

TABLE III. NORMAL RAT PLASMA: 1 ML. INTRAPERITONEALLY EVERY 8 HOURS FOR 72 HOURS

GROUP III (10 RATS)	AVERAGE	RANGE
Total body weight	214	184-235
Weight of excised liver	5.1	4.2-5.5
Calculated weight of residual liver	2.5	2.1-2.7
Calculated weight of total liver	7.6	6.3-8.0
Weight of liver after 72 hours	5.1	4.1-5.7
Calculated weight of liver regenerated	2.6	1.9-3.1
Calculated per cent of hepatic regeneration	51	38-65
		SD 7.2

Groups IV, V, and VI.—The results in these 3 groups of animals indicate that no inhibiting factor is present in distilled water, 0.9 per cent sodium chloride solution, or in a plasma expander (Plasmoid). The average degree of regeneration in each group, 76 per cent, 75 per cent, and 77 per cent, respectively, does not vary significantly from the value of the control untreated group (Table IV).

Groups VII and VIII.—The inhibiting effect of heterogenous types of plasma upon liver restoration is shown by these two groups. The injection of pooled normal bovine plasma resulted in 51 per cent regeneration, while the injection of pooled normal human plasma produced 53 per cent regeneration. These values are significantly different from the control group and correspond to the degree of regeneration obtained when pooled normal rat plasma was injected (Table V).

TABLE IV. EFFECT OF DEIONIZED WATER, 0.9 PER CENT SODIUM CHLORIDE, AND PLASMOID (1 ML. INTRAPERITONEALLY EVERY 8 HR. FOR 72 HR.) ON HEPATIC REGENERATION

	DEIONIZED H_2O (GROUP IV, 10 RATS)		0.9 PER CENT NaCl (GROUP V, 10 RATS)		PLASMOID (GROUP VI, 10 RATS)	
	AVERAGE	RANGE	AVERAGE	RANGE	AVERAGE	RANGE
Total body weight	209	177-244	218	194-235	208	191-232
Weight of excised liver	4.4	3.8-5.5	5.1	4.4-5.7	4.2	3.6-4.6
Calculated weight of residual liver	2.2	1.9-2.7	2.5	2.2-2.9	2.1	1.8-2.3
Calculated weight of total liver	6.6	5.7-8.2	7.6	6.6-8.9	6.2	5.4-6.9
Weight of liver after 72 hr.	5.5	4.8-6.3	6.3	5.4-7.7	5.2	4.4-5.7
Calculated weight of liver regenerated	3.3	2.9-3.8	3.8	3.2-4.8	3.2	2.6-3.6
Calculated per cent of hepatic regeneration	75	65-83 SD 6.1	75	66-82 SD 5.2	77	67-90 SD 7.4

TABLE V. EFFECT OF BOVINE AND OF HUMAN PLASMA (1 ML. INTRAPERITONEALLY EVERY 8 HR. FOR 72 HR.) ON HEPATIC REGENERATION

	BOVINE PLASMA (GROUP VII, 10 RATS)		HUMAN PLASMA (GROUP VIII, 10 RATS)	
	AVERAGE	RANGE	AVERAGE	RANGE
Total body weight	214	189-248	215	200-239
Weight of excised liver	4.8	3.5-6.7	4.7	4.2-5.5
Calculated weight of residual liver	2.4	1.7-3.3	2.1	2.1-2.7
Calculated weight of total liver	7.2	5.2-10.0	7.1	6.9-8.2
Weight of liver after 72 hr.	4.8	3.8-6.1	4.8	4.4-5.5
Calculated weight of liver regenerated	2.4	1.8-2.8	2.5	2.1-3.0
Calculated per cent of hepatic regeneration	50	41-60 SD 6.3	53	46.8-60.9 SD 5.2

Groups IX and X.—The significant difference in hepatic regeneration, resulting from the injection of plasma from patients without cancer and plasma from patients with cancer, is exhibited by these two groups (Tables VI and VII). The amount of regeneration obtained in each of the subgroups of Group IX agrees with results obtained in Group VIII. The injection of plasma from patients with cancer did not inhibit liver regeneration, and the findings in each of the subgroups of Group X, are comparable to those in the untreated control group.

Groups XI and XII.—When pooled plasma from patients without cancer and from patients with cancer was injected in double the volume employed in the previous groups, the difference in effect of the two types of plasma was most striking. Group XI rats, which received plasma from patients without cancer, had 49 per cent regeneration, while Group XII animals showed 91 per cent regeneration (Table VIII).

DISCUSSION

Two theories have been advanced to explain the phenomenon of hepatic regeneration in the white rat following partial hepatectomy. Glinos and Gey[5]

TABLE VI. PLASMA FROM PATIENTS WITHOUT CANCER (1 ML. INTRAPERITONEALLY EVERY 8 HR. FOR 72 HR.)

PATIENT NUMBER	SEX, AGE, AND DIAGNOSIS	RAT NUMBER	TOTAL BODY WEIGHT	WEIGHT OF LIVER REMOVED	CALCULATED WEIGHT OF RESIDUAL LIVER	CALCULATED WEIGHT OF TOTAL LIVER	WEIGHT OF LIVER AFTER 72 HR.	CALCULATED WEIGHT OF LIVER REGENERATED	CALCULATED PER CENT OF HEPATIC REGENERATION	AVERAGE PER CENT OF REGENERATION
1	M, 62	1	187	4.2	2.1	6.3	4.4	2.3	55	
	Tuberculosis	2	184	4.6	2.3	6.9	4.4	2.1	46	
		3	183	4.1	2.0	6.1	4.2	2.2	54	51
2	F, 58	4	203	4.8	2.4	7.2	5.0	2.6	54	
	Diabetes	5	218	5.0	2.5	7.5	5.0	2.5	50	
	controlled with insulin	6	210	4.8	2.4	7.2	4.7	2.3	48	51
3	M, 34	7	209	4.7	2.3	7.0	4.7	2.4	51	
	Empyema	8	215	4.8	2.4	7.2	4.9	2.5	52	
		9	202	4.3	2.1	6.4	4.3	2.2	51	52
4	M, 59	10	222	4.3	2.1	6.4	4.5	2.4	56	
	Anthrosilicosis,	11	230	4.4	2.2	6.6	4.7	2.5	57	
	emphysema, tuberculosis	12	225	4.3	2.1	6.4	4.3	2.2	51	53
5	M, 70	13	197	3.8	1.9	5.7	3.9	2.0	53	
	Wound infection	14	212	4.2	2.1	6.3	4.1	2.0	48	
	following herniorrhaphy, arthritis	15	226	4.4	2.2	6.6	4.3	2.1	48	49

TABLE VII. PLASMA FROM PATIENTS WITH CANCER (1 ML. INTRAPERITONEALLY EVERY 8 HR. FOR 72 HR.)

PATIENT NUMBER	SEX, AGE, AND DIAGNOSIS	RAT NUMBER	TOTAL BODY WEIGHT	WEIGHT OF LIVER REMOVED	CALCULATED WEIGHT OF RESIDUAL LIVER	CALCULATED WEIGHT OF TOTAL LIVER	WEIGHT OF LIVER AFTER 72 HOURS	CALCULATED WEIGHT OF LIVER REGENERATED	CALCULATED PER CENT OF HEPATIC REGENERATION	AVERAGE PER CENT OF REGENERATION
1	M, 62	1	248	5.3	2.6	7.9	6.5	3.9	74	
	Carcinoma of left	2	243	5.2	2.5	7.7	6.3	3.8	73	
	lung with abscess	3	247	5.6	2.7	8.3	7.0	4.3	77	75
2	M, 77	4	205	4.5	2.2	6.7	5.8	3.6	80	
	Carcinoma of left	5	211	4.4	2.2	6.6	5.5	3.3	75	
	lung with metastasis, tuberculosis	6	195	4.6	2.3	6.9	5.6	3.3	72	76
3	M, 61	7	231	5.2	2.5	7.7	6.5	4.0	77	
	Carcinoma of stomach with metastasis	8	207	4.7	2.3	7.0	6.1	3.8	81	
	to regional nodes	9	188	3.9	1.9	5.8	4.8	2.9	74	77
4	F, 56	10	229	5.1	2.5	7.6	6.2	3.7	73	
	Carcinoma of the	11	225	4.4	2.2	6.6	5.9	3.7	84	
	transverse colon	12	223	4.8	2.4	7.2	5.8	3.4	71	76
5	F, 44	13	250	5.1	2.5	7.6	6.7	4.2	82	
	Carcinoma of breast,	14	219	5.6	2.7	8.3	7.5	4.8	86	
	bilateral with axillary metastasis	15	249	6.2	3.0	9.2	7.9	4.9	79	82
6	F, 62	16	205	4.7	2.3	7.0	5.7	3.4	72	
	Carcinoma of descending colon	17	226	5.4	2.6	8.0	6.5	3.9	72	
	with hepatic metastasis, carcinoma of breast	18	194	5.1	2.5	7.6	6.5	4.0	78	74
7	F, 32	19	202	4.6	2.3	6.9	5.0	2.7	59	
	Carcinoma	20	187	5.3	2.6	7.9	6.6	4.0	76	
	of breast	21	180	3.3	1.6	4.9	5.0	3.4	103	79
8	M, 63	22	250	5.6	2.7	8.3	6.8	4.1	73	
	Carcinoma of lung,	23	234	5.1	2.5	7.6	6.5	4.0	78	
	tuberculosis, anthrosilicosis	24	223	4.8	2.4	7.2	5.8	3.4	71	74
9	M, 52	25	237	5.2	2.5	7.7	7.3	4.8	92	
	Carcinoma of sigmoid colon with	26	239	4.8	2.4	7.2	7.0	4.6	96	
	metastasis to regional nodes	27	188	3.8	1.9	5.7	5.7	3.8	100	96
10	M, 68	28	187	4.5	2.2	6.7	5.9	3.7	82	
	Carcinoma of lung	29	212	4.6	2.3	6.9	5.9	3.6	78	
	with invasion of pericardium	30	180	4.1	2.0	6.1	5.3	3.3	81	80

TABLE VIII. EFFECT OF PLASMA (2 ML. INTRAPERITONEALLY EVERY 8 HR. FOR 72 HR.) FROM PATIENTS WITH AND WITHOUT CANCER ON HEPATIC REGENERATION

	POOLED PLASMA FROM PATIENTS WITHOUT CANCER (GROUP XI, 5 RATS)		POOLED PLASMA FROM PATIENTS WITH CANCER (GROUP XII, 10 RATS)	
	AVERAGE	RANGE	AVERAGE	RANGE
Total body weight	191	165-235	193	159-225
Weight of excised liver	4.2	3.5-4.9	4.6	3.4-5.3
Calculated weight of residual liver	2.0	1.7-2.4	2.3	1.7-2.6
Calculated weight of total liver	6.2	5.2-7.3	6.9	5.1-7.9
Weight of liver after 72 hr.	4.1	3.3-4.9	6.5	5.0-7.4
Calculated weight of liver regenerated	2.1	1.6-2.5	4.2	3.3-4.8
Calculated per cent of hepatic regeneration	49	46-52 SD 2.5	91	79-98 SD 5.7

believe that certain constituents of normal serum exert a growth inhibitory action at their normal concentrations. Partial hepatectomy results in a decrease in the serum concentration of these constituents and this, in turn, initiates the regenerative growth of the liver. Christensen and Jacobsen[3] postulate that a circulating cell-stimulating substance may be present in serum following partial hepatectomy, and account for the increase in hepatic cellular mitosis and liver mass. However, these investigators showed that growth hormone had no influence on regeneration of the liver and they could demonstrate neither a growth-inhibiting substance in the liver of normal rats, nor a growth-stimulating substance in the remnant of hepatic tissue following partial hepatectomy.

The data of Groups IV, V, and VI indicate that neither the volume of fluid injected, nor isotonic salt solution, nor plasma expander have any effect upon hepatic regeneration when compared to the untreated control series. The results obtained in Groups VII and VIII indicate that the factors involved in the inhibition of hepatic regeneration are not species specific. These findings agree with those of Marshak and Walker,[8] who demonstrated that heterogenous chromatin from bovine and rabbit cells altered the rate of mitosis in the remnant of rat liver.

Following partial hepatectomy, the rat harbors a site of accelerated mitosis, a hepatic remnant whose cells are dividing at a rate comparable to the rate of mitosis in most tumors.[7] A patient afflicted with a malignant lesion also possesses a site of accelerated mitosis. Data from Group X reveal that the periodic injection of 1 ml. of plasma from such patients does not inhibit regeneration, while the same amount of plasma from patients without cancer does decrease the rate of regeneration of liver. It thus appears that certain constituents of the plasma are altered in patients with cancer. Whether this alteration is a decrease in mitosis-inhibiting substance or an increase in cell-stimulating substance cannot be determined from a comparison of Groups IX and X.

Additional information as to the factors involved may be obtained from the results in Groups XI and XII. When the amount of injected material is doubled, one of two possibilities could occur. If the difference in hepatic regeneration is mediated through a cell-inhibiting substance, then doubling the

volume of plasma injected should decrease the rate of regeneration in those animals receiving pooled plasma from patients with nonmalignant diseases, while those animals receiving the double dose of pooled plasma from patients with cancer would exhibit either no effect or a slight inhibitory effect upon hepatic regeneration. Conversely, if the difference is mediated through a cell-stimulating substance not present in normal serum or present in small concentrations and possibly buffered by cell-inhibiting substances, then animals receiving pooled plasma from patients with nonmalignant diseases would show either no change or a slight increase in the hepatic regeneration when compared to animals receiving one-half the volume of plasma from the same source. Likewise, if the difference is due to a cell-stimulating substance present and unopposed by inhibiting substances in the plasma of patients with a malignant lesion, then increasing the volume of such plasma injected should stimulate mitosis and regeneration of liver mass when compared to animals receiving one-half the volume from the same source.

Groups IX and XI exhibit a degree of regeneration which is approximately the same. However, there is a striking difference in the per cent regeneration in Groups X and XII. Group XII animals exhibited a significant increase in the amount of hepatic regeneration as compared to the rats in Group X. This suggests that the plasma of patients with cancer contains a substance which stimulates cell division, while the plasma of patients with nonmalignant diseases does not seem to contain such cell-stimulating substances. Further observations are needed to amplify and confirm the results reported in this pilot study. Among the implications of this study might be numbered the need for further investigations into the applications of this data as a tool in a screening test for malignancy, in investigations into the tumor-host relationship, and in studying the metabolic alterations associated with a malignant lesion.

SUMMARY

1. The regeneration of rat liver after partial hepatectomy was not inhibited by periodic intraperitoneal injections of demineralized water, isotonic salt solution, or plasma expander, but was inhibited by injections of pooled normal rat, bovine, and human plasma.

2. The periodic intraperitoneal injection of 1 ml. of plasma from patients with nonmalignant diseases inhibited liver regeneration while similar injections of plasma from patients with cancer did not inhibit regeneration.

3. The injection of 2 ml. of pooled plasma from patients without cancer did not further inhibit regeneration, but 2 ml. of pooled plasma from patients with cancer increased the rate of hepatic regeneration to a significant degree.

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THROMBOSIS AS THE CAUSE OF DELAYED DEATH IN DOGS THAT SURVIVED ACUTE CIRCULATORY FAILURE

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SINCE Schiff in 1876[6] massaged the heart effectively for the first time and restored circulation after cardiac standstill, there have been many reports of successful resuscitation following this most serious of complications during anesthesia. Many papers have been written on this technique contributing to the standardization of the method of resuscitation, which is now used with few variations in all hospitals.

At present the necessity of an open airway and the importance of early rhythmic compression through a wide thoracotomy are generally known. The time elapsed between acute circulatory failure and assisted circulation and breathing of oxygen is a decisive factor in increasing survival rates and reducing the number of permanent sequelae in the nervous system. Inadequate ventilation during anesthesia accounts for cardiac arrest in most clinical cases and prolonged anoxia of the nervous system has been blamed as the immediate cause of death.

The purpose of this paper is to demonstrate the occurrence of thrombosis in the vessels of vital organs, and the consequent tissue necrosis in the brain, lungs, and kidneys of dogs that survived 5 days or more after cardiac standstill. The heart has not been included in this study because of the direct injury caused by the surgeon at the time of compression during resuscitation.[5]

MATERIAL

Thirty-seven mongrel dogs of different sex and weight were subjected to experimentation. The circulation was stopped for periods of 5 or more minutes before resuscitative measures were applied. In general it was difficult to restore the circulation of these dogs. No pathologic findings have been demonstrated on postmortem examination of viscera of dogs which did not recover or died in the immediate postoperative period.[1, 2] Therefore only 10 dogs which survived 4 to 5 days are the subject of this paper.

METHOD

All dogs were anesthetized with sodium pentobarbital, and a Magill tube fitted into the trachea for the administration of oxygen at the time of the resuscitative measures. A left thoracotomy was performed through the fourth

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or fifth intercostal space, the lungs collapsed when the pleura was opened, and the animals which had been breathing room air during this part of the procedure became anoxic. After 5 to 8 minutes of hypercapnia, the heart showed some rhythm changes. One or two minutes later the blood pressure dropped to zero. The electrocardiograph registered almost normal tracings, but the asystolic period was so prolonged that it made circulation impossible. Timing of the 5 minutes of circulatory arrest began at this moment. Immediately thereafter, resuscitative measures were applied, that is, oxygenation of the lungs and rhythmic manual compression of the heart. After 2 or 3 heartbeats were perceived, 3 ml. of 10 per cent sodium lactate was injected into the left ventricle, followed by 2 ml. of 1/10,000 epinephrine. This technique was effective in all nonfibrillating hearts. Restoration of the circulation was complete in 2 to 5 minutes. Those cases that showed a depression in the blood pressure before the end of the operation were given an extra dose of epinephrine or Neo-Synephrine. The dogs which did not die within the following 5 days were sacrificed. The viscera were carefully examined, both macro- and microscopically, for obstructive circulatory lesions.

RESULTS

The end results of the operations are shown in Table I. The mortality rate of dogs which developed fibrillation in the operating room was very high; most died within 24 hours after the operation. Lack of adequate postoperative care may have been one cause of this great mortality.

TABLE I

	NUMBER OF DOGS	OPERATIVE DEATHS	EARLY DEATHS	5-DAY SURVIVORS
Fibrillation	16	12	3	1
Normal heartbeats	21	0	12	9
Total	37	12	15	10

The 10 surviving dogs showed the same characteristic picture: blindness, spasmodic contractures of the spinal muscles, and great rigidity of the limbs. They were not able to drink water or take food, and all had lesions of the brain stem. The medulla oblongata was especially damaged; some dogs showed necrosis of the posterior half in the closed part, while most of them had lesions in the upper part of the floor of the fourth ventricle (Fig. 1). Many other dark spots were found in the pons, cerebellum, and cerebrum (Fig. 2). Three dogs had pulmonary infarction, and one a large kidney lesion (Fig. 3). Microscopic examination showed thrombi in the lumen of the vessels with consequent areas of necrosis in the surrounding tissue (Figs. 4 through 7).

DISCUSSION

It is generally accepted that prolonged anoxia of the nervous system is the cause of early death after cardiac standstill. Even though this explains deaths which occur in the operating room or in the immediate postoperative period, it does not account for the occurrence of delayed death and sequelae.

Fig. 1.

Fig. 2.

Fig. 3.

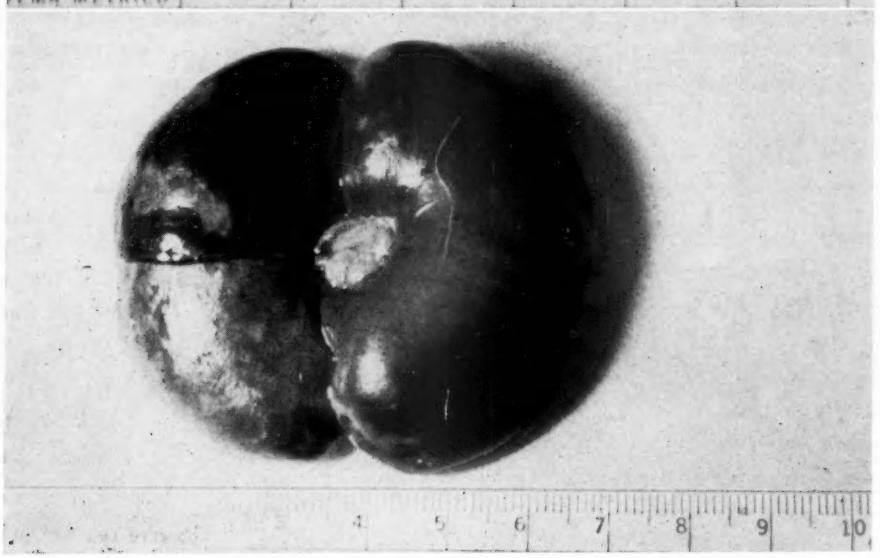


Fig. 1.—Cross section of the open part of the medulla oblongata showing necrotic areas in the floor of the fourth ventricle.

Fig. 2.—Graded sections of the brain stem with multiple necrotic lesions.

Fig. 3.—Kidney displaying a large infarct.

Fig. 4.

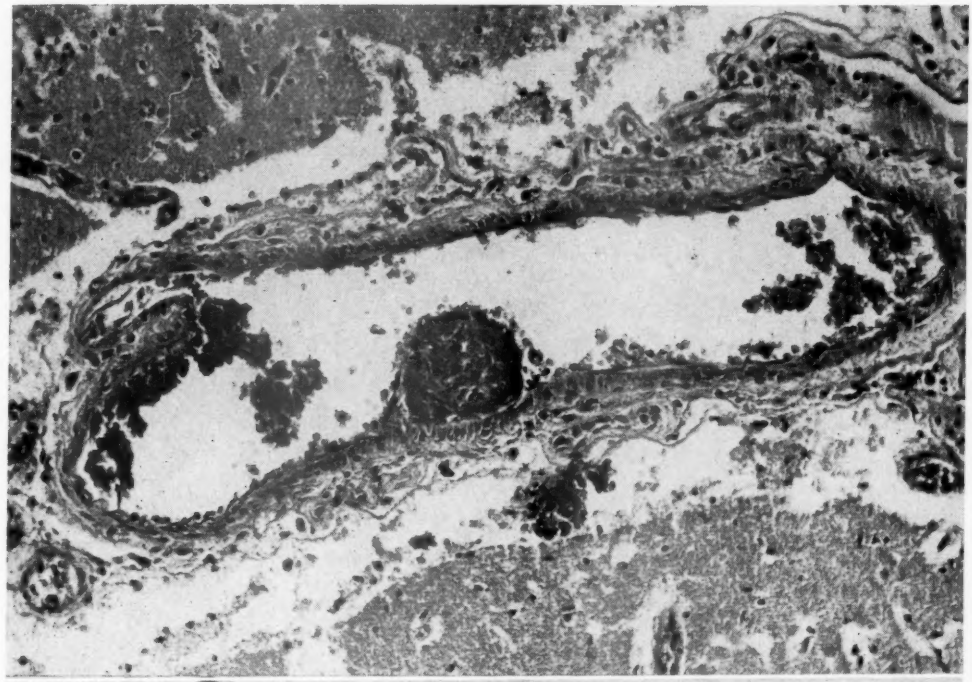


Fig. 5.

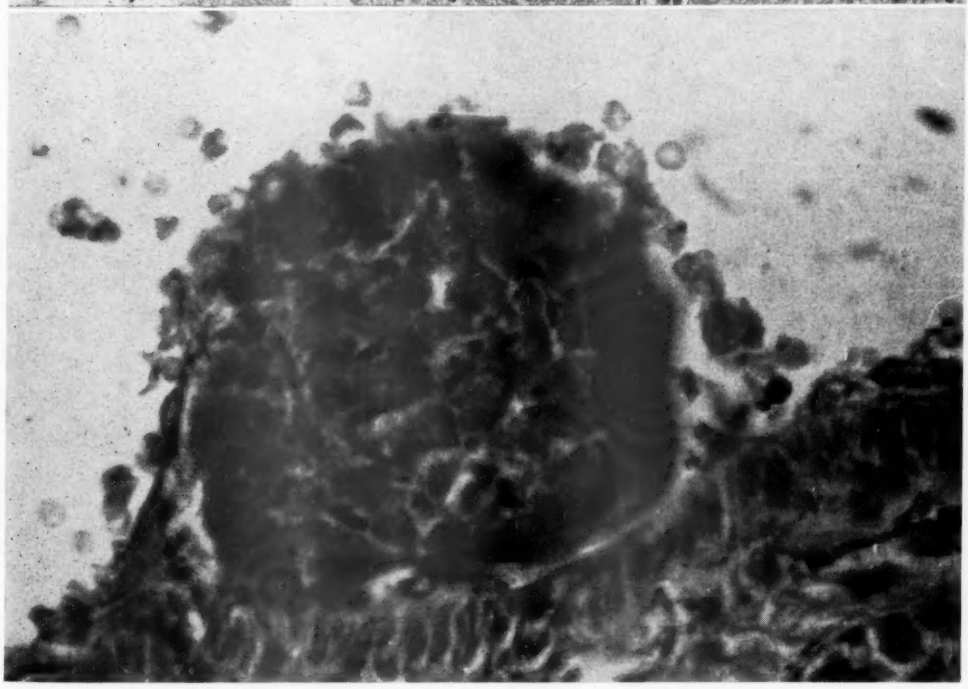
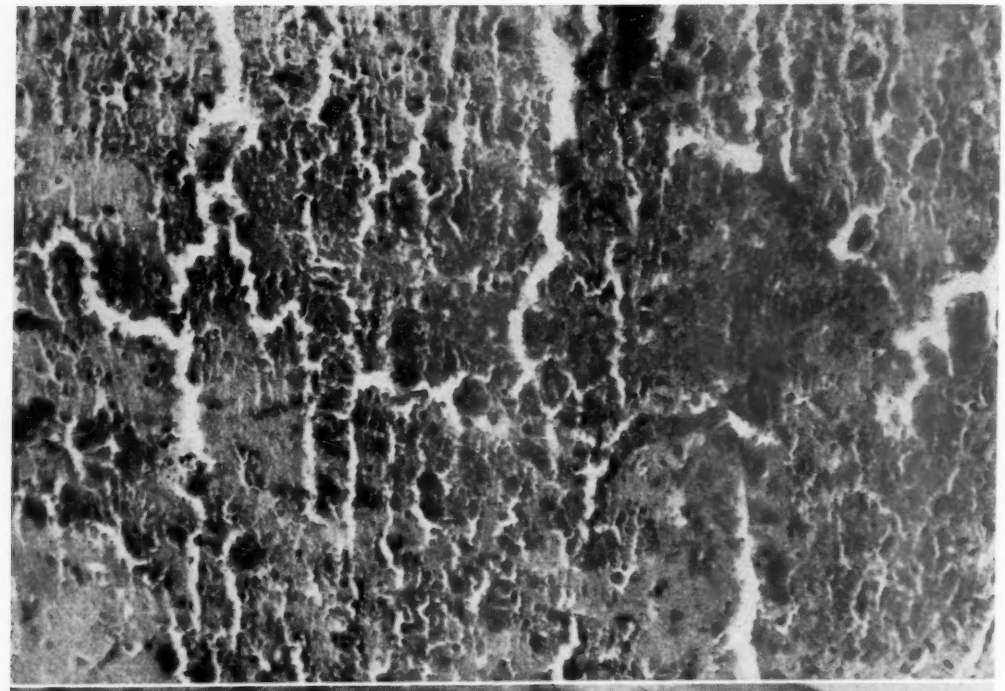


Fig. 4.—Section through the medulla oblongata. A small well-organized thrombus can be seen adhering to the vessel wall.

Fig. 5.—A higher power view of the thrombi shown in Fig. 4.

Fig. 6.



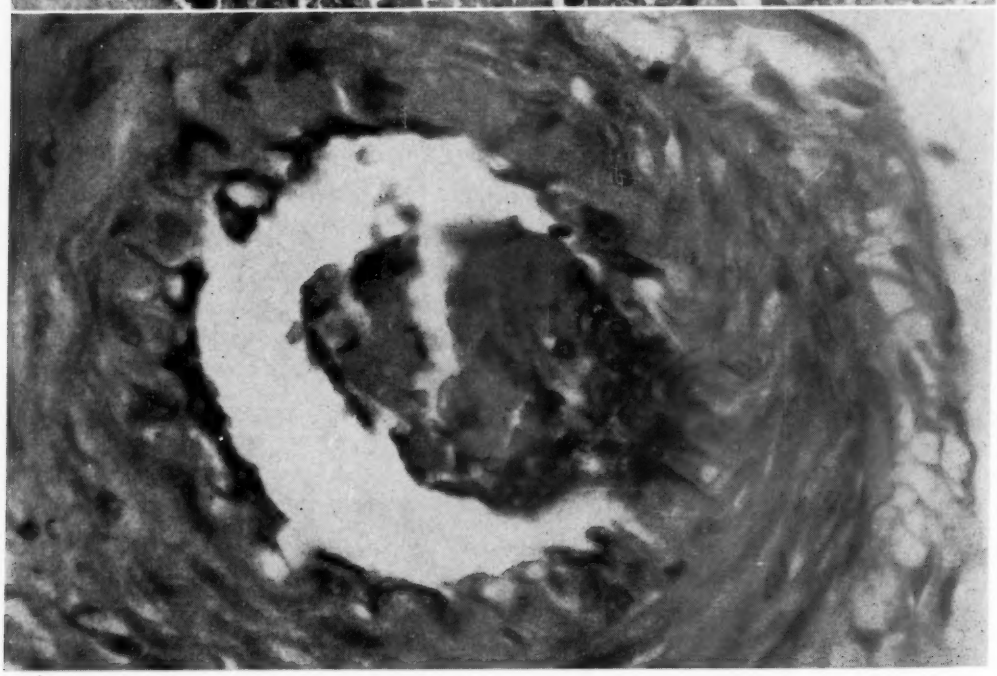


Fig. 7.

Fig. 6.—The resulting hemorrhagic infarct in an area distal to the thrombosed vessel demonstrated in Fig. 4.

Fig. 7.—Renal arteriole largely occluded by thrombi.

In the present work brain thrombosis has been proved to be a consequence of circulatory failure. This fact, as well as the thrombi found in the lungs and the kidney, explains in an acceptable way the symptoms of the patient who, after resuscitation, lives from several days to a few months with loss of consciousness, hyperthermia, hyperreflexia, convulsions, respiratory complications, and impairment of urinary excretion: the clinical picture of a cerebrovascular accident.

Crowell and associates[3, 4] described changes in the blood coagulation time of dogs in which cardiac arrest was produced. They were able to demonstrate microscopic clots in the blood of the vena cava as the result of this decrease in blood coagulation time.

In general blood coagulation is increased by trauma, presumably as a protection against hemorrhage. The decrease in blood coagulation time and stasis in the veins of the calf are recognized contributing causes of phlebothrombosis in the lower limbs.

The maximum blood pressure readings we have obtained either in the laboratory or with patients in the operating room have never been higher than 70 mm. Hg. Evidently, cardiac massage is a poor substitute for a normal heart to support an active circulation. Furthermore, stasis occurs in the veins and small terminal arteries and either emboli or thrombi may be produced. It would appear that treatment of cases that survive cardiac arrest should be active and similar to that of cerebral thrombosis resulting from other causes. This suggests that anticoagulants should be tried as an adjuvant therapy in cases of cardiac arrest.

SUMMARY

Experimental circulatory arrest was produced by means of anoxia in 37 dogs. A standard method was used and the effects on the 10 dogs which survived 5 days are reported. The anatomic findings indicate that thrombosis is responsible for the symptoms shown by the experimental dogs. Lesions occurred most frequently in the brain, but the lungs and the kidneys were also seriously affected. The results suggest that anticoagulant therapy should be tried as a supplementary measure in the treatment of cardiac arrest in human patients.

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AN IMPROVED SUMP SUCTION DRAIN FOR THE MANAGEMENT OF GASTRIC AND INTESTINAL FISTULAS

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GASTRIC or intestinal fistulas following abdominal surgical procedures probably do not occur as frequently now as in years gone by, but the care of such lesions still poses difficult problems and the associated morbidity continues to be prolonged. Excoriation of the skin surrounding the fistulous opening by digestive ferments in the fluid drainage has stimulated the design of various types of suction drainage systems for the control of this condition. Both flexible and rigid tubes have been employed for this purpose, each enjoying in its time a varying degree of popularity.

From the standpoint of engineering, it would seem that some application of the principle of the sump pump is necessary for the efficient control of the drainage fluids. Other desirable features of such a drainage system would be: (1) relative stability of the apparatus to allow for some degree of movement by the patient, (2) simplicity of operation, (3) ease of adjustment with respect to angle of insertion and depth of insertion of the drainage tube, and (4) provision for flushing of the suction tube to free it of obstructing matter. We have attempted to incorporate all these features in a new rigid sump pump drain patterned after the flexible rubber tube designed by Buyers[1] in 1957. The tube is held in any desired position by a specially constructed light weight stabilizer as illustrated in Fig. 1.

APPARATUS

The Drainage Tube.—The tubes are constructed of tough transparent cellulose acetate butyrate with 1/16 inch wall thickness and are 6½ inches in length and 7/16 inch in diameter at the widest point. The aspirating tip, however is 5/16 inch in diameter. It may on occasion be convenient to have several tubes of various sizes available, but up to the present time our clinical experience indicates that the size herein illustrated functions very satisfactorily. A side arm is provided for connection to a source of suction. At the distal tip of the tube, multiple side openings are provided through which the drainage secretions may be aspirated as well as through the end of the tube itself. Running through the lumen of the drainage tube from above the level of the side arm to the distal tip is a second small caliber tube which allows for the constant escape of air at the tip of the outer tube when suction is applied to the side arm. This inner tube can also be used for flushing the drain and the fistulous tract

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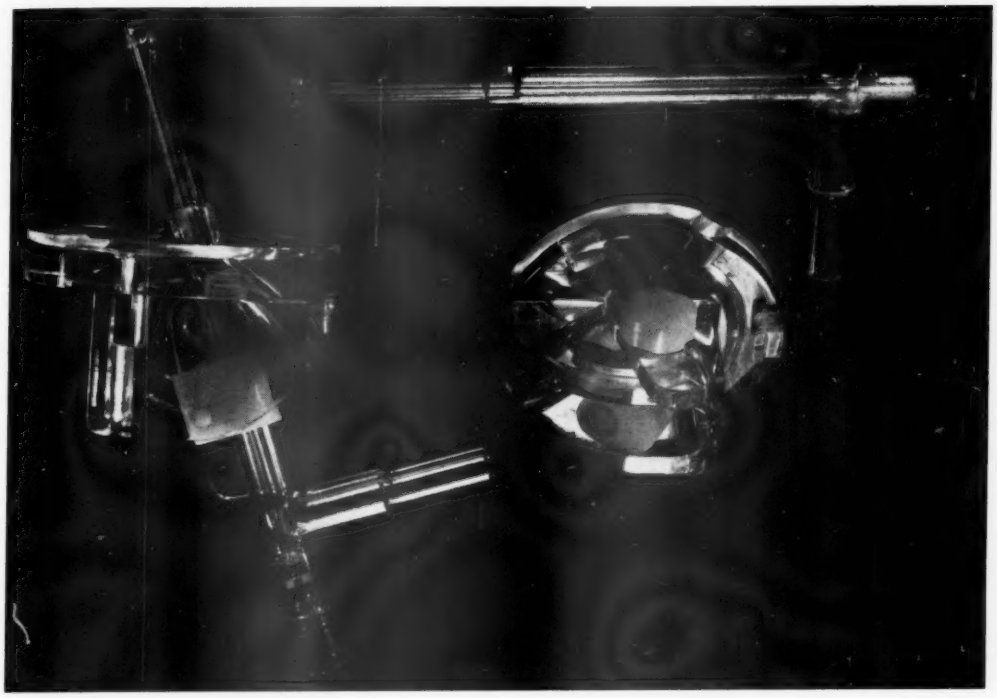

Fig. 1.—Photograph of the tube and stabilizer separate and assembled. Details of construction are available upon inquiry.

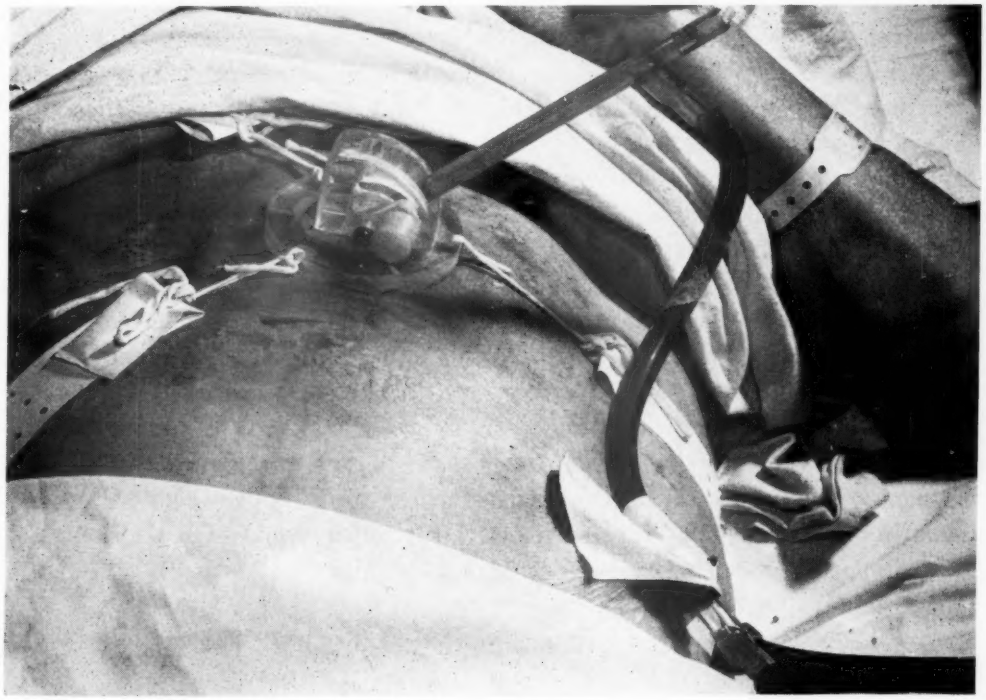

Fig. 2.—Photograph of the sump suction drain in position and functioning.

if the secretions are unusually thick. This can be accomplished either momentarily with a syringe or constantly by a drip of water or saline solution.

The Stabilizer.—The stabilizer is made of Plexiglas with a round base ½ inch thick which is provided with a central opening to accommodate the drainage tube. The vertical perforated portion is provided with a slot which allows a nylon screw swinging on a pivot to fasten securely the drainage tube by pressure on a collar at any desired height and angle indicated as proper by the opening of the fistula. If desired, flexible rubber drainage tubes can be used with this stabilizer by first fitting over them a snug short rigid sleeve at the point where the screw impinges. Three perforations from the side of the base to its upper surface serve as tie points to hold the stabilizer firmly in place on the patient's abdomen when bias tapes fastened to pieces of adhesive tape are attached (Fig. 2).

USE AND OPERATION

The simplicity of this equipment is such that, once it is positioned, a cooperative patient can tend it and even make minor adjustments himself to assure the greatest efficiency. Initially the size, depth, and direction of the fistulous tract should be determined. The stabilizer is centered over the cutaneous opening of the fistula and anchored in place with ties of bias tape or bandage to adhesive straps placed remote from the area. The suction tube is then inserted into the fistula to the desired depth and locked into position by tightening the thumb screw on the vertical part of the stabilizer. The side arm of the drainage tube can then be connected to a source of constant suction. Any of the small suction pumps available for clinical use are satisfactory for this purpose if a trap bottle is provided for the collection of the drainage. When used properly, none of the drainage fluid spills over the wound edge so that no dressings or ointment to protect the skin are necessary. Excoriations heal rapidly and the patient's comfort and morale are greatly enhanced. A reasonable amount of movement by the patient is possible without fear of interfering with the operation of the drain. A light sheet may be placed over the entire assembly if desired, but the use of a light cradle to support the bed clothes will probably be more satisfactory. As the fistula heals the drainage tube can gradually be withdrawn and set at a progressively higher level. If the secretions being aspirated are thick in consistency, their evacuation may be facilitated by dripping water or other fluid through the small central tube. In most instances, however, it has proved satisfactory to allow this tube to function merely as an air vent to prevent the surrounding tissues from occluding the aspirating holes and interfering with the suction action. Whenever necessary the drainage tube can be removed from the stabilizer, thoroughly cleaned, and replaced.

During the past 6 months, the described equipment has been used at the Buffalo General Hospital in the care of 7 patients with gastrointestinal fistulas. In each instance the care of the patients was greatly facilitated and necessary nursing care minimized. Skin excoriations have either been prevented or,

when already present, healed rapidly after treatment was begun. Five of these seven fistulas followed gastric resections, three being from the duodenal stump and two from the gastrojejunal anastomosis. One fistula followed an end-to-end anastomosis of the jejunum and one was due to the involvement of the duodenum by a malignancy.

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PLACEMENT OF A MATTRESS SUTURE IN ONE STROKE BY SIMULTANEOUS PASSAGE OF TWO NEEDLES

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THE second component of a mattress suture may, in most situations, be placed without a precisely accurate relationship to the location of the first needle bite, and without regard to reducing time to an absolute minimum. When it is essential that both strands of a horizontal mattress suture be aligned with meticulous precision, this requirement may be met by employing (a) a suture swaged onto an atraumatic needle at each end, and (b) a needle holder capable of grasping both needles simultaneously. This maneuver would also effectively reduce the time consumed in placing the suture, by eliminating the need for disengaging the first needle, then closing the needle holder on needle number two, and separately passing that portion of the stitch.

A practical example of this problem was encountered in developing a technique for plication of the noncoronary cusp area at the base of the aorta in the treatment of aortic insufficiency associated with dilatation of the base of the aorta. After a considerable period of trial and error in operations on dogs, a plan of procedure was devised which was executed successfully in a human case on March 4, 1959.[1] A series of mattress sutures was placed across the noncoronary cusp area, each suture being passed through an aorta rendered less tense and bloody than normal by brief periods of cardiac venous inflow occlusion, under normothermic conditions (Fig. 1). The need for passing each suture in the shortest possible time, and with both needles in exact alignment, was met by designing a special needle holder.†

The conventional needle holders can engage only one needle at a time, because of the angle of closure of the jaws, and this is also true of double-action needle holders. In the present instance the solution was provided by inserting a short sloping copper shelf on the lower jaw, and reducing the over-all jaw length by about 50 per cent (Fig. 2). Two needles can then be accommodated snugly, one before and the second behind the shelf. Since these sutures were to be tied over Ivalon pillows, to prevent subsequent cutting through the aorta, greater stability was supplied to the needle points by positioning the Ivalon on the needles before passing the stitch (Fig. 3).

While this instrument has been applied satisfactorily both in the laboratory and in a clinical case, there is considerable need for improvement. The use of needles of different sizes, or the development of a needle holder in which the

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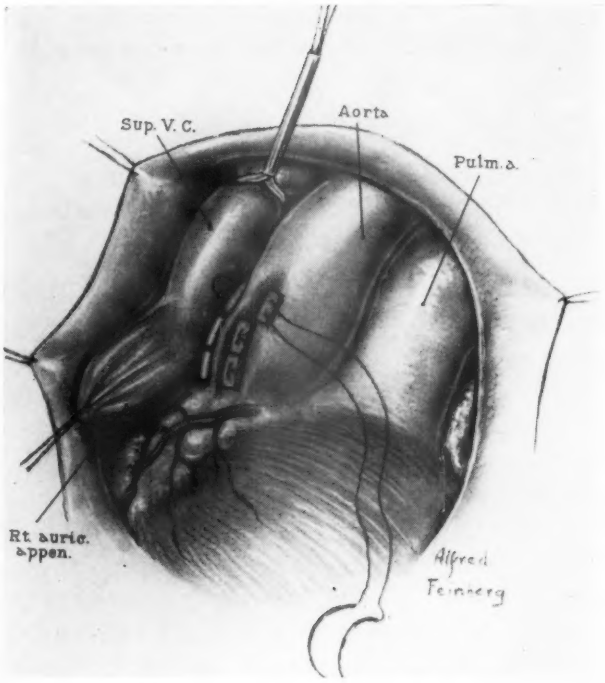

Fig. 1.

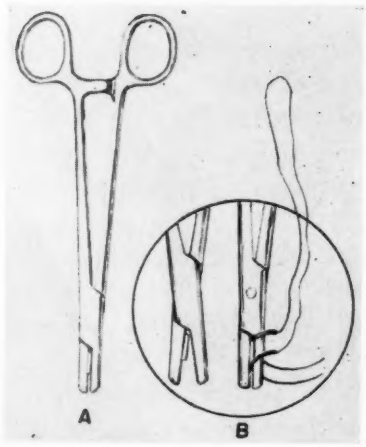

Fig. 2.

Fig. 1.—Plication of noncoronary cusp area at base of aorta by series of mattress sutures.
Fig. 2.—Needle holder modified to grasp two needles simultaneously.

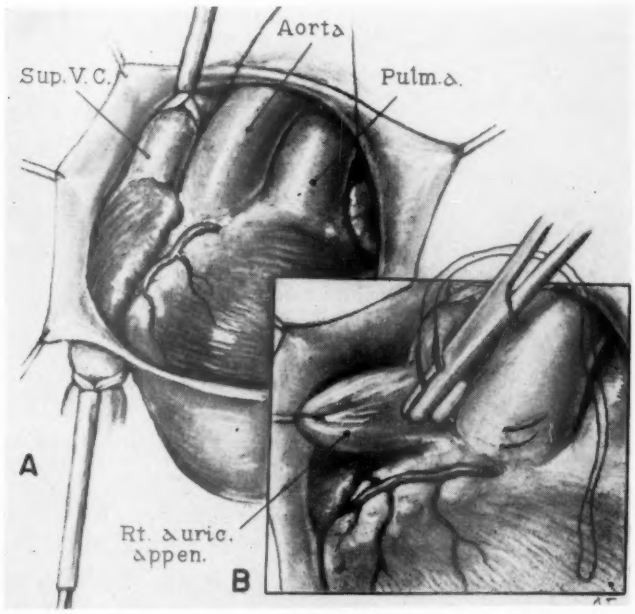

Fig. 3.—Stabilizing needle points by mounting Ivalon pillow before passing suture.

jaws would be parallel, are possible suggestions. It is felt that many other potential applications for this principle of the simultaneous passage of both components of a mattress suture will be found. The present need has been met by the instrument described.

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MALIGNANT TUMORS OF THE UPPER JAW

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THE treatment of malignant tumors of the maxilla imposes difficult decisions upon the responsible physician. Radical surgery may cause disfigurement as well as the loss of an eye. The same may also be said of extensive radiotherapy. Less drastic treatment may result in recurrence of the growth with subsequent loss of life. What course of treatment can be offered the patient that will yield the highest percentage of cures and a low mortality rate? As with the less frequent neoplasms elsewhere, individual experience is necessarily limited in scope. Recourse must be made to the results obtained in the treatment of large groups of patients over a sufficient period of time so that the value of each therapeutic policy can be measured against the yardstick of the long-term cure rate. The results of treatment of patients with malignant tumors of the maxilla in the Columbia-Presbyterian Medical Center during the past 18 years form the basis of this report.

This paper will deal primarily with malignant epithelial tumors arising in the maxillary sinus. Other malignant tumors arising in the maxilla will be classified for the sake of completion but no conclusions as to the efficacy of treatment can be drawn as these are too few in number. Excluded will be tumors originating from the palatal mucosa of the maxilla since these should be properly studied as part of the group of oral cavity carcinoma. As will be readily appreciated there will be occasional difficulties in ascertaining the exact site of origin in certain cases, such as, tumors originating in the ethmoids or nasal cavity. However, an attempt has been made to include only maxillary tumors as based upon the physical examination of the patient as recorded in the hospital chart.

HISTORICAL BACKGROUND

Malignant tumors of the nasal cavity and accessory sinuses were known to the ancients. In his extensive discourse on malignant tumors of the maxilloethmoidal area, Ohngren[18] presents this phase of medical history in scholarly detail. Of interest is the recorded Hippocratic admonition that cancerous tumors should not be treated at all, because every known therapeutic measure merely helped shorten the patient's life. Inadequate surgery of malignant tumors today shall testify to the aptness of this observation.

The earliest removal of a tumor of the upper jaw recorded in English, according to Woodman,[30] dates back to 1671 when a Richard Wiseman described the operation in these words:

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A man about 28 years of age came out of the country with a cancer on his left cheek stretching itself from the side of his nose close under the lower eyelids to the external canthus, so making a compass downwards. It was broad in its basis, and rose, capped like a sugar loaf. The cancer threatened his eye with inflammation, and he hastened up and importuned me to undertake it. I complied with his desire, and four or five days after, having prepared all things ready, the actual cautery, digestives, desensitives, and bandages, I pulled the tumor towards me with one hand and made my incision close to the eyelid and cut it smooth off. Then viewing our work and observing some relic of cancer remaining above the external canthus, we consumed it by actual cautery and dressed the wound with our digestives, with embrocation, desensitives and moderate bandages.

In 1879 Walsham[27] reported a resection of a tumor of the upper jaw which resulted in a cure. With the growth of understanding of cellular pathology in the latter part of the nineteenth century, the elementary foundation blocks for the study of malignant tumors of the maxillary area were secured, and therapeutic results could be rationally compared and evaluated. With the advent of the twentieth century many surgical avenues of approach were tried in an attempt to extirpate antral tumors, but the results, in terms of recurrence and high postoperative mortality, were discouraging.

Because of the high operative mortality associated with open surgical attacks on tumors of the upper jaw and with the increased use of x-ray and radium in malignant diseases, other modalities of treatment were developed. In this country, the experience in the use of soldering irons and radium implantation at the Mayo Clinic was summarized by New in 1926[16] and again in 1935.[17] During the latter part of this period surgical diathermy was used in place of soldering irons. In 1935 New[17] was able to report on 295 patients with a 5-year cure rate of 47 per cent. Interestingly, the 10-year cure rate drops to 29 per cent; whether this is due to the appearance of late metastases or the failure to get follow-up reports cannot be ascertained by the data presented in the paper. However, as with malignant tumors elsewhere, the possibility of recurrence, even after periods of time exceeding 10 years, is ever present. Wille[28] in his study of malignant tumors of the maxillary sinus reports 3 patients who died of their malignancy after having been free of any clinical signs of recurrence for 21, 14½, and 12½ years, respectively. Truly these are unusual cases, but certainly reports on survivors of less than 5 years' duration cannot be taken as the basis for support of a specific type of treatment.

In Europe, especially in Scandinavia, there developed great interest and experience in the use of electrosurgery in the treatment of malignant tumors of the maxilla. This was combined with the application of radium into the affected tissue as well as the use of teleradium in certain instances. According to Ohngren[18] two advantages accrued with the substitution of electrosurgery for "cold steel" surgery: (1) Shock and postoperative mortality were greatly lessened. (2) The coagulated tissue sealed lymph and vascular channels forming an effective barrier to the dissemination of tumor cells and infection. With this therapy Ohngren was able to report in 1933 a 5-year cure of 38.5 per cent of all patients thus treated, and 30.8 per cent 5-year cure of all patients admitted to the Sabbatsberg Clinic and Radiumhemmet with malignant tumors of the maxilloethmoidal area whether treated or not.

In 1954 Larson and Martensson[10] brought up to date the results obtained in Sweden treating malignant maxillary tumors with preliminary radiotherapy, electrosurgery, and radium. Of 114 patients so treated they were able to report a 5-year cure rate of 45 per cent. When all patients who were admitted to the author's institution were considered, the 5-year cure rate dropped to 27 per cent. Of interest is the fact that in patients whose disease was thought too far advanced for the combined surgical and radiotherapy approach, radiotherapy alone produced a 5-year cure rate of 9 per cent. It should be noted, however, that a few miles away in Norway results of the combined surgical and radiotherapy procedures as reported by Wille[28] yielded a 5-year cure rate of only 18 per cent. Be that as it may, the 45 per cent 5-year cure for carcinoma of the maxillary antrum as obtained by Larson and Martensson[10] stands in bright relief against the dark picture usually painted for this neoplasm.

The use of radiotherapy alone after a biopsy is, at present, reserved for the inoperable cases by most clinics treating carcinoma of the upper jaw. There have been some rather interesting reports, however, of respectable 5-year cure rates using radiotherapy alone. The French evidently have had the most success of this sort. In 1935 Regato[22] reported 40 per cent 5-year cures in a small series of epitheliomas of the maxillary sinus. Baclesse[2] more recently has had a 31 per cent 5-year cure rate. However, in a group of 18 patients treated by radiotherapy in this country for carcinoma of the maxilla Lenz[11] reported only 2 survivors alive at 7½ and 17 years after treatment. Tod,[25] in her study of 68 patients in Great Britain with carcinoma of the maxillary antrum treated by radium implantation alone, had an over-all 5-year cure rate of 24 per cent.

With the improvement of anesthetic methods and the availability of blood replacement, interest in surgical excisions of maxillary tumors became popular again. The ideal of surgical therapy for malignant tumors is wide excision of the primary growth resected en bloc with the draining lymph nodes. However, anatomic necessity often imposes compromises upon the surgeon, and these compromises are reflected in an increased recurrence rate. Schall,[23] in discussing tumors of the paranasal sinuses, states: "The ideal removal of any cancerous growth is made through normal tissue. This is absolutely impossible in a region such as the nasal sinuses. Here the removal amounts to a curettage. The operation is ideal for disseminating the growth and producing either distant metastases or local recurrences." The problem of local recurrences is a particularly distressing one as it is an overt sign of the inadequacy of the surgical measure employed. In addition since we know from the studies of Braund and Martin[3] that at autopsy 60 per cent of patients with tumors of the nasal sinuses do not have widespread disease, this surgical failure is a particularly grievous one.

Because of difficulties encountered with complete surgical extirpation, it is quite common to recommend a combined surgical and radiotherapeutic approach to this disease. Lynch[12] and Collins and Pool[5] highly recommend combined surgical and x-ray therapy to control this carcinoma but offer no statistics to bolster their claims. Likewise a report by Raines and James[20] that advocates surgical extirpation followed by intercavitary radium fails to give follow-up

figures on the results of this therapy. Tabb[24] in his lengthy and detailed article on radical extirpation of the maxilla states: "The best therapeutic results are being achieved with a combination of surgery and postoperative irradiation." Yet in his own series of 20 cases treated by this method during the period 1940 to 1955, 15 patients were dead, 2 dying, one untraced, and 2 surviving 4 or more years—a cure of 10 per cent. These results cannot be classified, I believe, as satisfactory. It should be noted that it is cold steel surgery that is recommended not electrosurgery.

Wilson[29] reporting from Great Britain states that it is best to irradiate the area before any surgery is done on the suspected antral tumor, including biopsy. He further states that in 33 per cent of cases no tumor is found histologically on the material removed from the antrum. This of course raises the question of whether or not tumor was present at all before radiotherapy was given. Castigliano[4] in a recent report uses heavy preoperative external radiation (5,000 to 10,000 r.) and then performs a maxillectomy. From the statistics presented it is difficult to ascertain precisely what is the percentage of 5-year cures in patients treated by this method.

MATERIAL AND METHODS

All records of the Columbia-Presbyterian Medical Center with the diagnosis of a malignant tumor of the maxilla during the period 1940 to 1958 were reviewed. Only those cases in which there was a pathologic report of a malignant tumor were accepted in this series. Both ward and private patients are included in this report. It should be noted that this hospital can be somewhat selective in its admission policy and thus patients with obviously hopelessly advanced malignancies are generally not accepted for treatment. No patient shall be considered cured of the malignancy until a follow-up period of at least 5 years has demonstrated absence of all signs of local disease or distant metastases. Thus, in the group of patients treated from 1953 to 1958 while there may be definite failures, there can be no definite cures.

PATHOLOGY

In considering the pathologic features of the malignant tumors of the maxilla it is obvious that they may arise from the epithelial lining of the maxillary sinus, or the bony framework that surrounds the sinus. In addition there are tumors of hematogenous or lymphogenous origin. In the present series the histologic types that were found are summarized in Table I.

The retinal anlage tumor of the maxilla was first reported by Halpert and Patzer[7] in 1947. Further cases of this rare maxillary tumor were reported by Traube and Martin.[26] No final decision has been given as to the malignant propensities of these tumors because of the limited number of cases so far reported. No such tumor was found in this present series. Perhaps somewhat related pathologically, is a case of a neuroblastoma of the maxilla as reported by Armbrecht and Waterman.[1] However, in the patient described, examination was not sufficiently complete to rule out the possibility of this being a metastatic deposit rather than a primary tumor.

TABLE I. PATHOLOGIC CLASSIFICATION OF MALIGNANT MAXILLARY TUMORS IN 68 PATIENTS

HISTOLOGIC TYPES	NUMBER OF PATIENTS
Squamous cell carcinoma	49
Adenocarcinoma	1
Mucoepidermoid carcinoma	5
Cylindroma	3
Lymphosarcoma	1
Reticulum cell sarcoma	3
Osteogenic sarcoma	2
Myxoma	2
Multiple myeloma	1
Sarcoma (type undetermined)	1
	68

In the present series there were 2 patients with osteogenic sarcoma of the maxilla. They were both treated by resection of the maxilla. No long-term follow-up data are as yet available. Chondrosarcoma of the maxilla has been reported by Paterson[19] as a rare pathologic entity in a patient with multiple osteochondromas.

Myxoma of the maxilla has been reported by Hovnanian[9] as an isolated case report in which one patient was treated by radical maxillectomy with a good short-term follow-up. Two patients in the present group had a pathologic diagnosis of myxoma.

M. D. (No. 932540), a 28-year-old man, presented himself for treatment because of drawing sensation in the right eye. In November, 1948, x-ray revealed destruction of the floor of the right orbit. Through a Fergusson approach, a maxillectomy was performed. Tumor was left behind and this was cauterized. A radium pack was placed in the cavity 3 weeks postoperatively. The patient made a good recovery. The patient did quite well over the ensuing years. There was no recurrence of the tumor. He died suddenly of coronary occlusion in November, 1958.

The second patient with a myxoma of the maxilla was treated by surgical extirpation and represents a 5-year cure.

Holland[8] has recorded a plasmacytoma of the maxilla which responded very well to external radiotherapy. From the pathologic discussion following Holland's report, however, it is by no means certain whether the tumor was actually a plasmacytoma or a lymphoma. Of interest is a patient in whom the first manifestation of multiple myeloma was a maxillary tumor.

G. D. (No. 163407), a 54-year-old man, had the onset of pain in the left cheek in September, 1953. Several weeks later an upper tooth fell out spontaneously. He went to see his dentist who treated him unsuccessfully for several weeks. He was then referred for medical treatment because of sinus trouble. Biopsy of the mass found in the old tooth socket revealed a plasmacytoma. External radiotherapy was given. X-ray studies in 1954 revealed many areas of skeletal rarefaction in the clavicle, ribs, and long bones. He died in 1955 of widespread multiple myeloma.

In the present series there were 4 patients with "lymphogenous" tumors of the maxilla. There was one lymphosarcoma and three reticulum cell sarcomas. All were treated primarily by external irradiation. Only one patient of this group is alive and free of disease 8 years after treatment.

There are patients with metastatic carcinoma in the maxilla in whom the growth may masquerade as a primary maxillary tumor. The need for adequate and accurate histologic examination of the tumor as well as a complete history and physical examination prior to radical surgery or radiotherapy is self-evident. However, on occasion one cannot be certain if there are two distinct primary carcinomas or a metastatic focus of one primary tumor. There is one patient in the present series that illustrates this point very well.

M. M. (No. 579194), a 46-year-old woman, entered the Columbia-Presbyterian Medical Center because of pain in the right side of the face and epistaxis of 2 months' duration. X-ray studies revealed clouding of the right antrum. Three years prior to admission the patient underwent a left radical mastectomy at another hospital for carcinoma of the breast. Biopsy of the tumor mass in the antrum via a Caldwell-Luc revealed carcinoma. A maxillectomy was done several days later and upon pathologic examination no tumor was found. Despite the supposedly complete removal of the tumor at biopsy, there was local recurrence in the orbit as well as metastatic nodes in the neck 9 months later. This was treated by external radiation. The patient died 6 months after the x-ray therapy, and autopsy revealed widespread metastases to the lymph nodes in the supraclavicular, axillary, and mediastinal areas as well as lung, liver, and adrenals. There was no local recurrence in the maxilla or breast. Because of the variegated cellular pattern in the different metastatic foci, it could not be ascertained whether it was the maxillary or the mammary tumor that had metastasized so widely.

Another patient in this series died of a carcinoma of the pancreas 2 years after she had been treated for a carcinoma of the maxilla. However, in this instance, it was quite clear that these two malignant tumors were not related to one another.

ETIOLOGY

The etiology of malignant change in the maxilla remains obscure as it does elsewhere in the body. There are 3 patients in the present series in which an etiologic agent is suggested, namely, Thorotrast. MacMahon's[13] report was one of the first to indict Thorotrast as a neoplastic agent. In 1955 Guimares and associates[6] reviewed the literature and reported on some experimental work demonstrating the ability of Thorotrast to induce neoplastic changes. Most of the reports reveal sarcomatous change occurring in the hepatic endothelial cells where Thorotrast is stored. However, there are also cases of squamous carcinoma accredited to Thorotrast.

Three patients in this present series have histories of Thorotrast studies of their sinuses years prior to the development of carcinoma of the maxillary antrum. These patients have been studied in detail and reported by Rankow, Lattes and Kligerman.[21]

E. B. (No. 297612), a 38-year-old white man, entered the hospital with a 4-month history of retro-orbital pain. Twenty years previously he had had Thorotrast injected in the right antrum for study of sinusitis. Biopsy revealed the presence of a squamous cell carcinoma as well as residual Thorotrast. A right maxillectomy including exenteration of the orbit was performed. Follow-up examination at 5 years reveals no evidence of recurrent carcinoma.

L. J. (No. 956249), a 32-year-old white woman, entered the hospital with a 2-month history of pain in the right upper jaw. Ten years previously she had a thorium compound

put in the right antrum for study of the sinus. Work-up including a biopsy revealed the presence of an adenocarcinoma. The right maxilla was resected. Pathologic examination confirmed the presence of an adenocarcinoma. Examination 4 years postoperatively reveals no evidence of recurrence.

L. T. O. (No. 062632), a 70-year-old white man, was admitted to the hospital because of pain in the left molar area. Thirteen years previously he had had Thorotrast put into the left antrum for radiologic study. X-ray examination revealed clouding of the left antrum as well as the presence of a mucoepidermoid carcinoma. At present he is undergoing radiotherapy.

The danger of Thorotrast is well recognized now, but here is the unfortunate example of 3 patients, two of them quite young, who had been exposed to this compound many years previously. These 3 patients then went on to develop carcinoma of the maxillary antrum 40 years, 20 years, and 13 years after their exposure to the radioactive substance.

A long history of chronic sinusitis was found in a fair percentage of patients with malignant tumors of the maxilla. However, the number of people who suffer from sinusitis in the greater New York area is legion, and the number who develop carcinoma of the maxilla is small. Therefore, no conclusion can be drawn as to the etiologic relationship between the two conditions.

ANALYSIS

There were 68 patients who were accepted as having malignant tumors of the maxilla in the present series. The sex distribution was reversed as compared to other reports[17, 20] in that there was a somewhat greater incidence in females than in males. This is illustrated in Table II.

TABLE II. SEX INCIDENCE OF MALIGNANT MAXILLARY TUMORS

	MALE		FEMALE	
	NUMBER	PER CENT	NUMBER	PER CENT
All cases	30	44	38	56
Squamous cell carcinoma	23	47	26	53

Table III depicts the age distribution of the patients studied. As can be seen malignant maxillary tumors strike primarily the upper age groups although youth is no guarantee of immunity.

TABLE III. AGE INCIDENCE IN DECADES OF MALIGNANT MAXILLARY TUMORS

PATIENT'S AGE	20-30	31-40	41-50	51-60	61-70	71-80
All patients	4	5	12	23	15	9
Squamous cell epithelioma	3	3	10	16	10	7
Female	0	1	5	9	6	5
Male	3	2	5	7	4	2

TREATMENT AND RESULTS

These are the most difficult and important figures to review because the rationale of any cancer therapy is based upon the percentage of long-term cures. In the present series the therapy was dictated by the clinical condition

of the individual patient as interpreted by the surgeon in charge of the case. No set therapeutic regimen was employed. In a clinical arrangement of this type, patients with far-advanced disease received radiotherapy as their only treatment because surgical excision was obviously out of the question. In a similar fashion when the surgeon knew that tumor was left behind, postoperative radiation was employed in an attempt to sterilize the field. Thus the patients treated by surgery alone were those in whom the tumor was small, and complete surgical excision was at least theoretically possible. One, therefore, should constantly keep in mind this unconscious selectivity of the method of treatment in attempting to analyze the results.

The magnitude of the surgery is oftentimes difficult to ascertain. There appears to be a propensity among surgeons when dictating an operative report of a malignant condition to use the term "radical" even though at times it may amount to an extended biopsy. An attempt has been made to separate those patients in whom surgical excision was actually attempted and those in whom a curettage was done via a Caldwell-Luc opening. This latter group properly belongs to the radiotherapeutic group. The surgery used here is cold steel surgery. The electrocautery was used on occasion to control bleeding in difficult areas, but it was not used extensively as recommended by Ohngren[18] and Larson and Martensson.[10]

The results of the present series are listed in Table IV.

These figures reveal a 5-year cure rate of 15.9 per cent in patients treated for squamous cell epithelioma of the maxillary sinus. If all the malignant epithelial tumors of the maxilla are considered, the 5-year rate is 14 per cent.

TABLE IV. FIVE-YEAR CURE RATE OF MALIGNANT TUMORS OF THE MAXILLA

	NUMBER OF PATIENTS	DEAD	ALIVE WITH KNOWN RECURRENCE	5-YEAR CURE	NOT FOLLOWED	ALIVE LESS THAN 5 YEARS WITHOUT KNOWN RECURRENCE
Squamous cell epithelioma	47	22	9	7	6	3
Mucoepidermoid carcinoma	5	2	1	0	0	2
Cylindroma	3	1	1	0	1	0
Adenocarcinoma	1	0	0	0	0	1
	56	25	11	7	7	6

TABLE V. TREATMENT AND RESULTS OF MALIGNANT MAXILLARY TUMORS

	SQUAMOUS CELL CARCINOMA		MUCOEPIDERMOID CARCINOMA		CYLINDROMA		ADENOCARCINOMA	
	TREATED	CURED	TREATED	CURED	TREATED	CURED	TREATED	CURED
Surgery	8	2	0	0	1	0	0	0
Surgery and radiotherapy	24	3	3	0	1	0	1	0
Radiotherapy	14	2	1	0	1	0	0	0
No treatment	1	0	1	0	0	0	0	0
	47	7	5	0	3	0	1	0

The methods of therapy are listed in Table V. Here numbers are too few to allow for accurate statistical comparison. There appears to be no method, however, that consistently offers good results.

DISCUSSION

The treatment of cancer is a complex problem. As our knowledge of the natural history and growth patterns of neoplasms becomes more complete, it is evident that no single therapeutic approach should be recommended for all patients stricken with a specific malignant process. With the improvements in anesthesia, and the availability of blood and antibiotics, the surgical attack on carcinoma of the maxilla has become bolder. Operative mortality has shrunk to low levels. (There was only one operative death in the present series.) Unfortunately this has not reflected itself in improvement in the 5-year survival rate. Although many authorities[4, 5, 12, 20] recommend extensive cold steel surgery and radiotherapy, their own statistics fail to corroborate this mode of therapy as the best.

This study presents statistical findings that indicate that the results obtained by conventional surgery and radiotherapy do not achieve the long-term cure rates obtained by New[16, 17] 25 years ago using a soldering iron and radium. Likewise the 5-year cure rate of 45 per cent obtained by Larson and Martensson[10] using electrocautery technique and radiotherapy stands high above the results obtained in the present series. The number of patients in this present series is relatively small, and we recognize the inherent statistical fallacies in attempting to compare results of treatment in groups of patients at different institutions. Nevertheless, we believe that there is sufficient evidence to suggest that further experience should be obtained in this country in the therapeutic measures outlined by Larson and Martensson[10] in an attempt to raise our low long-term survival rates.

SUMMARY

1. The historical aspects of malignant maxillary tumors and various methods of therapy are reviewed.

2. Sixty-eight patients with malignant tumors of the maxilla are studied in terms of pathology, therapy, and long-term cures.

3. In the present series there were 56 patients with epithelial tumors of the maxilla.

4. The 5-year cure rate was 14 per cent.

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Pediatric Surgery

CONDUCTED BY MARK M. RAVITCH, M.D.

CONGENITAL BILIARY ATRESIA

I. ANALYSIS OF THIRTY CASES WITH PARTICULAR REFERENCE TO DIAGNOSIS

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CONGENITAL biliary atresia may best be diagnosed by combining an astute clinician and an accurate clinical laboratory. Unfortunately, no single test of liver function, nor any battery of tests, will distinguish this disease from other causes of neonatal obstructive jaundice with a sufficient degree of regularity, and the surgeon, and all too often the pathologist, must make the final diagnosis. This situation may be improved by a period of observation, but data pertaining to the optimal length of time these patients should be observed is not available in the literature.

Thirty proved cases of congenital biliary atresia were seen at the University of Minnesota Hospitals and at two affiliated hospitals during the period 1945 to 1958. The laboratory data in these cases were reviewed in an attempt to delineate possible clues in preoperative diagnosis. A group of patients who entered with jaundice as a principal manifestation of illness, but who subsequently were proved not to have biliary atresia, was used for comparison. This analysis confirmed earlier reports[10, 38] and our impression that clinical differentiation of prolonged obstructive jaundice in infancy may be exceedingly difficult at times. Points of particular value in differential diagnosis will be discussed.

Twenty-eight of our cases had extrahepatic biliary atresia and the remaining two had intrahepatic biliary atresia. In only two instances was there an extrahepatic atresia of a nature amenable to operation. One infant died of peritonitis and pneumonia 3 days after surgical correction, and in the other case the presence of a duct suitable for anastomosis was not recognized at the time of operation. This is in essential agreement with Swenson's[41] recent estimate that only 5 per cent of children with biliary atresia are actually cured by surgery.

METHODS

The case records at the University of Minnesota Hospitals, Minneapolis General Hospital, and Ancker Hospital (St. Paul), revealed that 30 cases of

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congenital biliary atresia had been diagnosed since Jan. 1, 1945. The majority of the cases (23) were seen at the University of Minnesota. The cases are listed in Table I.

All cases with jaundice persisting beyond 3 weeks of age that were seen at the University of Minnesota Hospitals during the period 1952 to 1958 were reviewed. A total of 24 consecutive cases were analyzed (Table II). The final chart diagnoses in these cases were cirrhosis (4), neonatal hepatitis (9), inspissated bile syndrome (5), inspissated bile syndrome following erythroblastosis fetalis (5), and undetermined (1).

TABLE I, *A*. CASES OF BILIARY ATRESIA, HOSPITALIZED 1945-1958

CASE NUMBER	HOSPITAL NUMBER	RACE	SEX	ONSET OF JAUNDICE	AGE AT OPERATION	EXTRAHEPATIC BILE DUCTS FOUND AT OPERATION	OPERATION
1	758033	W	F	4 wk.	2½ mo.	No hepatic ducts	Exploratory laparotomy
					4 mo.	Normal	Exploratory laparotomy
2	764988	W	M	3 days	3½ mo.	Complete absence	Exploratory laparotomy
3	766955	W	F	6-10 days	4½ mo.	Common bile duct atretic	Cholecystojejunostomy
4	788190	W	F	Birth	3½ mo.	Complete absence	External biliary drainage (no bile drained)
5	790533	W	F	2 wk.	5 mo.	Cords only	Exploratory laparotomy
6	793222	W	M	Birth	5½ mo.	Common bile duct absent	"Duct" connected to duodenum
7	795944	W	M	Birth	2½ mo.	Hepatics?	"Choledochoduodenostomy"
					4½ mo.	Complete absence	Internal biliary fistula
8	799853	W	F	Birth	2 mo.	Complete absence	Exploratory laparotomy
9	823645	W	M	5 wk.	5 mo.	Bulb at hilus	Bulb anastomosed to duodenum
					19 mo.	Complete absence	Exploratory laparotomy
10	826376	W	M	6 days	3 mo.	Atretic threads	Exploratory laparotomy
11	826751	W	M	2 days	3½ mo.	Complete absence	Exploratory laparotomy
12	829764	W	F	11 days	1½ mo.	Common bile duct 1 mm.	Choledochoduodenostomy; liver tissue implanted in cheek and jejunum
13	831172	W	M	1 mo.	5 mo.	Normal	Exploratory laparotomy
					6 mo.	Normal	Hepatoenterostomy
14	843385	W	M	3-4 days	3½ mo.	Complete absence	Exploratory laparotomy
15	852728	W	M	Birth	2½ mo.	Common bile duct cord, no hepatics	Exploratory laparotomy
16	887196	W	F	Birth	4½ mo.	Complete absence	Exploratory laparotomy
17	880593	W	F	---	---	---	None
18	910477	W	F	2 days	6 mo.	Common bile duct absent	"Hepatic ducts" anastomosed to duodenum
19	916401	W	F	Birth	7 mo.	Fibrous cords	Exploratory laparotomy*
20	920120	W	M	Birth	5 mo.	Complete absence	Exploratory laparotomy
21	920235	W	M	3 days	2½ mo.	Complete absence	Exploratory laparotomy
22	921239	W	M	7 wk.	4 mo.	Ducts fibrotic and atretic	Exploratory laparotomy
23	925375	W	M	20 days	---	---	None
24	A201806	W	F	Birth	8 mo.	"Threads" only	Exploratory laparotomy
25	A216176	W	F	Birth	1½ mo.	Complete absence	Exploratory laparotomy†
26	M26334	W	M	2-3 days	2 mo.	Normal	Exploratory laparotomy
27	M-A15974	W	M	15 days	---	---	None
28	M4571A	W	F	None	---	---	None
29	M4929A	W	M	---	3 mo.	No hepatics	Exploratory laparotomy
30	MA16537	I	F	5 wk.	3½ mo.	Cords only	Exploratory laparotomy

In column labeled "race," W= white and I= Indian.

*Operated upon at State University of Iowa Hospitals and operative note furnished through the courtesy of Dr. D. A. Ehmke, Department of Pediatrics.

†Operated upon at Children's Hospital, St. Paul.

TABLE I, *B*. RESULTS IN CASES OF BILIARY ATRESIA HOSPITALIZED 1945-1958

CASE NUMBER	BIOPSY	FOLLOW-UP	REMARKS
1	Normal architecture	Died 8 mo.	Acute purulent bronchitis and acute ulcerative colitis; hepatic ducts absent at autopsy
2	Marked cirrhosis	Died 2 days postoperatively	Intra-abdominal hemorrhages; no ducts at autopsy
3	Marked cirrhosis	Died 3 days postoperatively	Peritonitis and pneumonia; no common bile duct at autopsy, others patent
4	Slight fibrosis	Died 11 mo.	Ascites; no autopsy
5	Marked cirrhosis	Died 7 mo.	
6	---	Died 6½ mo.	No biliary ducts found at autopsy; subperitoneal hematoma with rupture
7	---	Died 8 days postoperatively	Imperforate anus; no autopsy
8	---	Died 2½ mo.	No bile in common bile duct at time of surgery; no autopsy but clinical congenital heart disease
9	Marked cirrhosis	Died 2⅔ yr.	Cyanotic congenital heart disease
10	Slight fibrosis	Icteric at 7 mo.	
11	Slight cirrhosis	Died 1$\frac{5}{12}$ yr.	
12	Moderate cirrhosis	Died 8 mo.	Thought to be inoperable at surgery; no autopsy
13	Intrahepatic biliary atresia	Died 3¼ yr.	Hepatojejunostomy unsuccessful; died of extradural hematoma, secondary to bleeding diasthesis; ventricular septal defect
14	---	Poor health 6 mo.	
15	Slight cirrhosis	Icteric at 18 mo.	
16	Moderate cirrhosis	Died at 11 mo.	
17	Normal architecture	Died 10 days	Complete atresia of bile ducts found at autopsy; also total anomalous pulmonary return, and bilateral talipes equinovarus
18	Marked cirrhosis	Died 7 mo.	No biliary ducts found at autopsy; pericardial effusion
19	Intrahepatic biliary atresia	Good health 16 yr.	Xanthomas, pruritus; normal cholecystogram at 14 yr.
20	Moderate cirrhosis	Icteric at 1 yr.	
21	Marked cirrhosis	Icteric at 10 mo.	
22	Moderate cirrhosis	Icteric at 7 mo.	
23	---	Died 33 days	Aspiration pneumonia; moderate cirrhosis and no bile ducts found at autopsy.
24	---	Died 12 mo.	No bile ducts and severe cirrhosis at autopsy
25	---	Died 7 mo.	Dilated common bile duct ending in a fibrous remnant found at autopsy
26	Slight fibrosis	Died 3¾ yr.	Thought that saline injected into gall bladder at surgery entered duodenum; no lumina in ducts at autopsy
27	---	Died 2½ mo.	Ventricular septal defect and imperforate anus (colostomy); bile ducts were fibrous cords and moderate cirrhosis found at autopsy
28	Normal architecture	Died 2 hr.	Complete absence of bile ducts at autopsy; ventricular septal defect and polycystic kidney; premature, 1175 grams
29	Marked cirrhosis	Died 10 mo.	7 or 8 large dilated bile "lakes" at hilus found at autopsy
30	Marked cirrhosis	Died 8½ mo.	

Laboratory techniques used were all standard procedures that have been reported previously.[12, 20, 22, 23, 28, 29, 36, 43]

Until April, 1949, serum cholesterol was determined by Bloor's[3] method; from April, 1949, to February, 1957, by the method of Schoenheimer[37] and

TABLE II. CASES OF PROLONGED JAUNDICE USED FOR COMPARISON

CASE NUMBER	INITIALS	AGE AT ADMITTANCE	SEX	DIAGNOSIS	SURGERY	OUTCOME AND REMARKS
1	K. O.	1 mo.	F	Cirrhosis	0	Died 6 wk.; moderate cirrhosis at autopsy
2	A. S.	2 mo.	M	Cirrhosis	Needle biopsy	Fair health at 6 mo.
3	H. W.	3 mo.	M	Cirrhosis	Exploratory laparotomy	Ascites and poor health at 1 yr.
4	L. G.	1 mo.	M	Cirrhosis	Exploratory laparotomy	Died 13 mo. subdural hematoma
5	J. S.	2 mo.	M	Hepatitis	0	Well at 3 mo.; mother had hepatitis 2 wk. before delivery
6	W. B.	2 mo.	M	Hepatitis	0	Fair health at 19 mo.; short stature and frequent upper respiratory infections
7	W. S.	2 mo.	M	Hepatitis	0	Well at 4 mo.; mother had severe infectious hepatitis 1 yr. before birth; BSP 20%, in first trimester of pregnancy
8	W. P.	3 mo.	M	Hepatitis	0	Rapid recovery
9	D. E.	2 mo.	M	Hepatitis	Exploratory laparotomy	Died 27 mo. with ascites and liver failure and eosphageal varices
10	J. B.	1 mo.	F	Hepatitis	Exploratory laparotomy	No follow-up
11	K. B.	4 mo.	M	Hepatitis	0	Died 4 mo. of bronchopneumonia
12	R. C.	4 mo.	F	Hepatitis	Exploratory laparotomy	No follow-up
13	M. P.	2 mo.	M	Hepatitis	Exploratory laparotomy	Well at 5½ mo.
14	M. B.	2 mo.	M	Inspissated bile	0	Well at 3½ mo.; Decholin therapy
15	K. S.	2 mo.	M	Inspissated bile	0	Well at 3½ mo.; $MgSo_4$ therapy
16	D. F.	2 mo.	M	Inspissated bile	0	Well at 4½ mo.
17	C. B.	1 mo.	F	Inspissated bile	0	?Residual cirrhosis at 6 mo.; Decholin therapy
18	P. C.	1 mo.	F	Inspissated bile	0	Well at 3 mo.
19	M. N.	2 mo.	M	Inspissated bile and erythroblastosis	0	Well at 7 mo.
20	E. W.	1 mo.	M	Inspissated bile and erythroblastosis	Exploratory laparotomy	Died 3½ mo. of bronchopneumonia
21	G. H.	Birth	F	Inspissated bile and erythroblastosis	Exploratory laparotomy	Well at 26 mo.
22	D. P.	8 days	F	Inspissated bile and erythroblastosis	0	No follow-up
23	C. H.	Birth	F	Inspissated bile and erythroblastosis	0	No follow-up
24	F. H.	2 mo.	M	Unknown	0	No follow-up

Sperry[37, 40]; and from February, 1957, to the present the method of Abell and associates[1] was used. Cholesterol, as determined by Bloor's method, is approximately 10 to 20 per cent higher than with the Schoenheimer-Sperry method, and the cholesterol determined by the method of Abell and his group gives

virtually the same readings as the Schoenheimer-Sperry method at lower serum levels, but may be up to 20 per cent higher when values over 300 mg. per cent are involved. Cholesterol values for these methods are graphed together in Fig. 6 using separate symbols.

Alkaline phosphatase was determined by Bodansky's[4] method until January, 1951, by the method of King and Armstrong,[19] from that date until May, 1956, and by the method of Kind and King[18] since then. The results of the latter two methods are comparable and are not separated for analysis in this report. Fecal urobilinogens were determined on either 24-hour or 4-day stool collections. Separate analysis showed no essential differences in calculating the results either in terms of urobilinogen per 24 hours or per 100 Gm. of feces and the data are presented together. Similarly for the purposes of this report, there was no obvious difference in analyzing separately reports in Ehrlich units (E.U.) or in milligrams of urobilinogen and the results are presented as Ehrlich units per 100 Gm. of feces.

RESULTS

Survival.—In only 2 cases in this group were biliary ducts present that were amenable to surgical correction. One of these infants died of pneumonia and peritonitis 3 days after a cholecystojejunostomy. In the other case, a dilated common bile duct, obstructed in the distal third, was found at autopsy, but not at a previous exploratory laparotomy.

Conversely, in 4 other instances, attempts were made at anastomosis although the subsequent course proved that the anomaly was not correctable. Necropsies in two of these proved that the atresia was complete, and in 2 cases, no extrahepatic ducts were found on re-exploration. A fifth case was thought to be inoperable at the time of original operation and macerated liver tissue was implanted into the jejunum and the right cheek in a vain attempt to prolong life.

Laboratory Data.—Fig. 1 presents the pattern of the total serum bilirubin determinations at various ages. These values range from a low of 4.0 mg. per cent to a high of 37.0 mg. per cent. There appears to be a slight rise in the mean values with age but individual examples are glaringly out of line. Furthermore, the range at any one age is so large that no simple correlation of total serum bilirubin and age can be made. Separate analysis of the one minute and 15 minute fractions show no essential differences from the data in Fig. 1.

Individual patterns of both total and one minute serum bilirubin determinations are shown in Fig. 2. All cases with three or more determinations are included. It is apparent from these graphs that no single pattern can be considered characteristic. Thus, the fourth patient with biliary atresia had a sharp rise and then an equally rapid fall, while the first, fifth, and eighth patients exhibited relatively stable bilirubin levels. Considering even shorter intervals, for example a single month or less, increases the hazards of drawing conclusions from serial bilirubin determinations.

Similar graphs for cases of cirrhosis, hepatitis, and the so-called inspissated bile syndrome are shown in Fig. 3. In these cases the bilirubinemia decreased over the months, in all except 2 cases. Since none of the patients with biliary atresia had total serum bilirubin levels less than 4.0 mg. per cent, this was selected as a basis for comparing the time of disappearance of jaundice. Considering the 24 patients without biliary atresia, levels above 4.0 mg. per cent were present throughout life in 2 cases, throughout the duration of observation in 2 cases (5 months and 12 months), and were never this high in one case. Five cases did not have a long enough period of observation to obtain detailed information on. This left 14 cases for analysis where the serum bilirubin decreased to less than 4.0 mg. per cent. This phenomenon occurred as early as 1½ months of age and as late as 6 months of age. The median time for declination to this level was 3 months. In most cases a period of observation of 6 to 8 weeks would have differentiated these infants as unlikely to have biliary atresia.

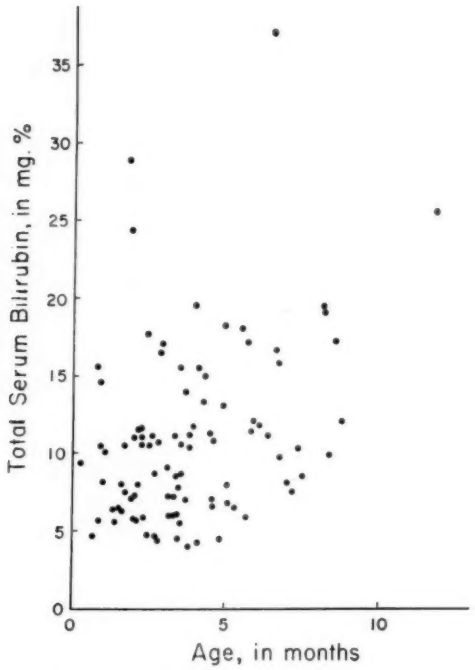


Fig. 1.—Total serum bilirubin determination at various ages in 28 cases of biliary atresia. Separate analysis of direct and indirect bilirubin levels revealed no essential differences.

Figs. 4 through 7 depict the variation of the cephalin-cholesterol flocculation, thymol turbidity, total serum cholesterol, and alkaline phosphatase values at various ages in congenital biliary atresia and the cirrhosis-hepatitis-inspissated bile group. There were no differences in the cephalin-cholesterol flocculation and thymol turbidity values for these groups. The number of cholesterol determinations in the latter group was small, but again there seems to be no clear-cut differentiation from the cases of biliary atresia. Values of

alkaline phosphatase levels of over 90 King-Armstrong units (4 cases) or over 20 Bodansky units (5 cases) were found only in the cases of congenital biliary atresia.

Excretion of fecal urobilinogen is shown in Fig. 8. The values in cases of congenital biliary atresia ranged from 0 to 6 E. U. per 100 Gm. of feces. In the cases without atresia, these ranged from 0 to 30.2 E. U. per cent, but there were only 7 determinations over 7.0 E. U. out of 36 determinations recorded.

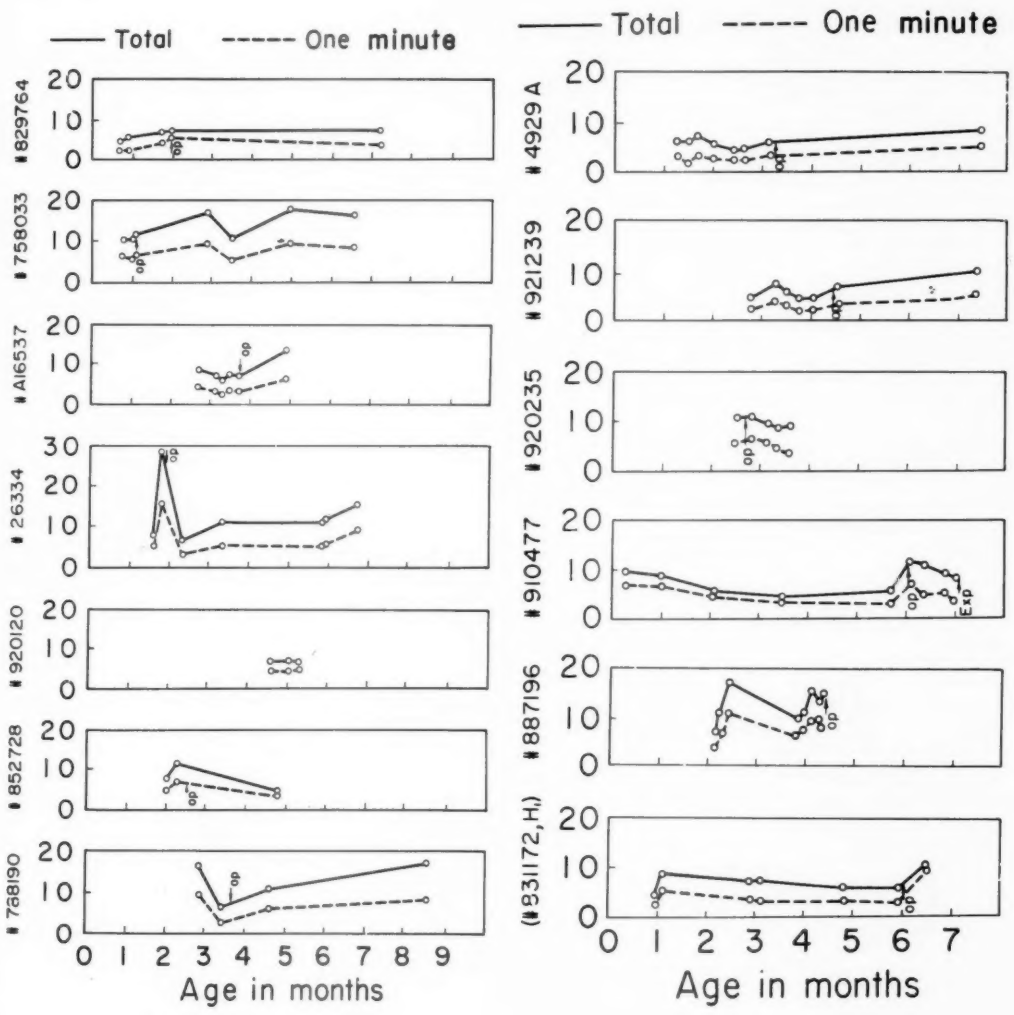


Fig. 2.—Patterns of serial bilirubin determinations in 13 patients with biliary atresia who had three or more determinations recorded.

Three determinations of total lipids were recorded for 2 cases of biliary atresia and 15 determinations on 9 cases without atresia. The values in the biliary atresia cases were 8, 12, and 13 units per milliliter. In the cases without atresia, the values ranged from 11 to 61, with a median of 27.

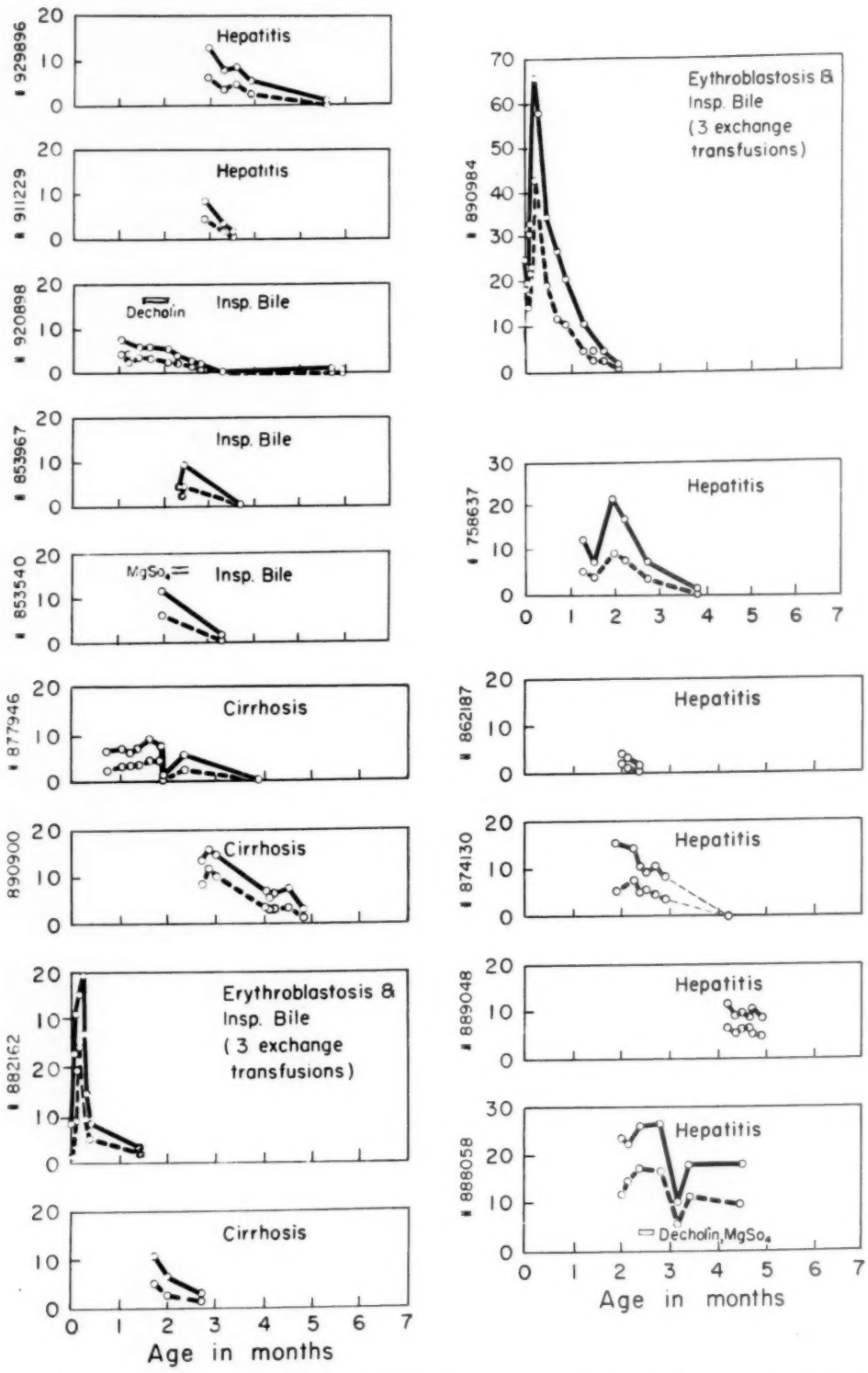
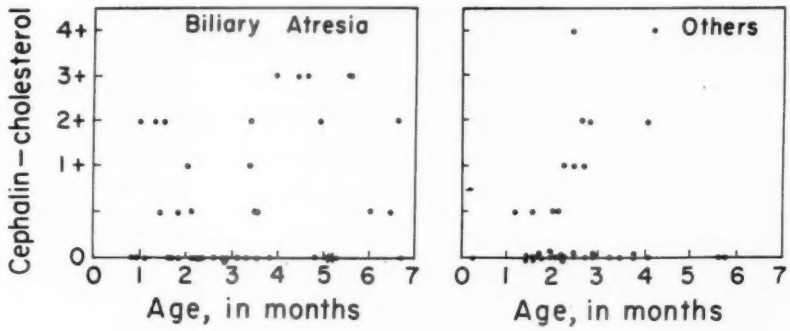


Fig. 3.—Patterns of serial bilirubin determinations in 15 infants with other causes of prolonged obstructive jaundice.

Fig. 4.



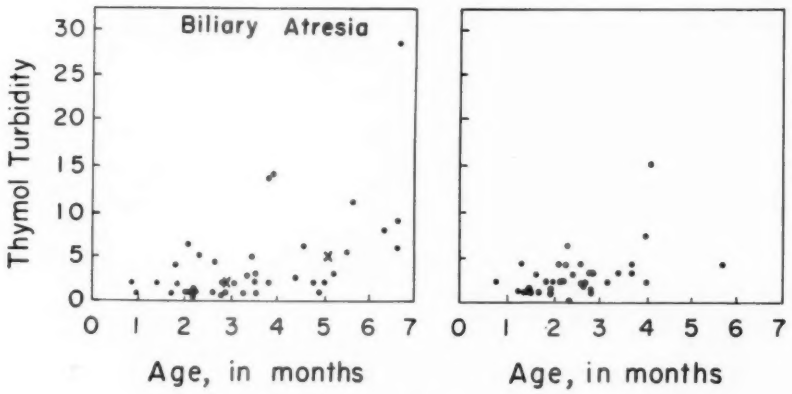


Fig. 5.

Figs. 4 and 5.—Cephalin-cholesterol flocculation and thymol-turbidity determinations at various ages in biliary atresia and other causes of prolonged obstructive jaundice. X denotes the results in one case of intrahepatic biliary atresia (Case 13).

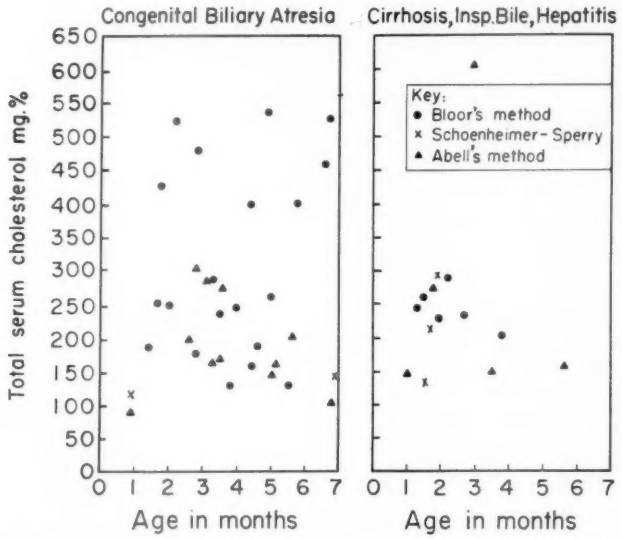


Fig. 6.—Total serum cholesterol determinations at various ages in biliary atresia and other causes of prolonged obstructive jaundice. See text for discussion of the various laboratory methods.

Zinc turbidity determinations were recorded in only one case of biliary atresia (4 units) and only 6 of the other cases (range 1 to 5 units).

Serum cholinesterase determinations were recorded twice for a single case of biliary atresia, 0.45 and 0.58 △ pH per hour. Six determinations, made in the cases without atresia, ranged from 0.29 to 0.96 △ pH per hour.

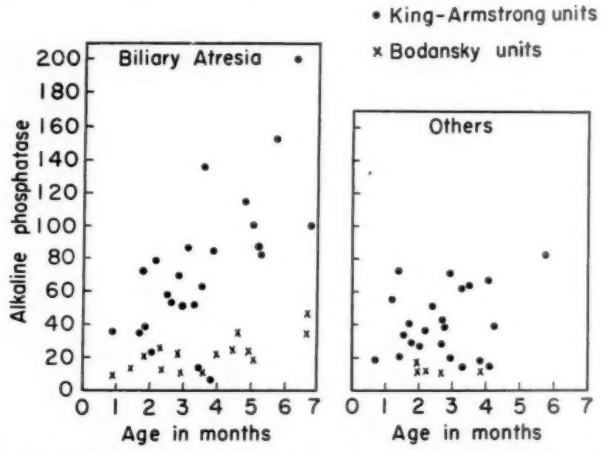


Fig. 7.—Alkaline phosphatase determinations at various ages in biliary atresia and other causes of prolonged obstructive jaundice. Results were higher in a few cases of biliary atresia for both the earlier Bodansky method and the more recent King-Armstrong method.

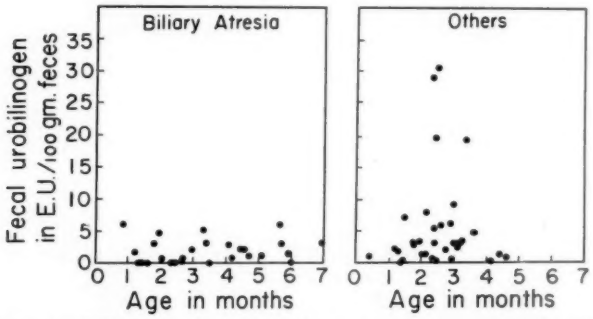


Fig. 8.—Fecal urobilinogen determinations at various ages in biliary atresia and other causes of prolonged obstructive jaundice. Separate analysis of the results showed no essential differences in calculating the results in terms of urobilinogen per 24 hours or per 100 Gm. of feces or in terms of Ehrlich units or milligrams and the data are graphed without further separation. Labeled as Ehrlich units per 100 Gm. of feces although the actual determinations were recorded by each of the four methods mentioned.

Serum transaminase levels (SGOT) were recorded only four times. In two instances of biliary atresia, these were 458 and 560 units, respectively. In one case of inspissated bile syndrome, two determinations were reported as 122 and 126 units.

Three attempts were made in patients with an inspissated bile syndrome to "flush" the biliary system with cholegogues. In two cases, the bilirubin levels decreased shortly after the cholegogues were used, while in the third case there was no clear-cut effect, probably because the total serum bilirubin levels were never over 2.4 mg. per cent.

DISCUSSION

Diagnosis.—Standard textbooks[2, 34] list among the differential diagnosis of biliary atresia such conditions as erythroblastosis fetalis, sepsis, syphilis,

and even physiologic jaundice. These conditions generally are easily differentiated by specific tests and by the passage of a few weeks. In infants with erythroblastosis fetalis who have had one or more exchange transfusions, Hsia[16] states that jaundice seldom persists after 7 days and never after 10 days. Infants with erythroblastosis who have had only small transfusions or who have been untreated are usually not jaundiced longer than 3 weeks. Similarly, infants with sepsis often appear ill and the jaundice usually resolves quickly with adequate treatment. Delaying operation until 4 to 6 weeks of age will eliminate these cases from consideration.

The association of erythroblastosis and biliary atresia has been frequently mentioned but there does not appear to be any etiologic relationship between the disease entities.[26, 27, 33, 39] It should be kept in mind that erythroblastosis can occur with biliary atresia and also that an obstructive type of jaundice may follow erythroblastosis.

The time of onset of clinical jaundice is of some diagnostic import, if care is used to elicit a period when physiologic jaundice has faded. Gellis[9] states that, "From our experience, diagnosis of atresia of the bile ducts is unlikely in infants who become clinically icteric on the day of birth." Myers and associates[32] found that the stated time of onset of jaundice was on the first day of life in 18 of 40 cases of proved extrahepatic biliary atresia seen at the Mayo Clinic. In Table I, it may be seen that in 10 of the 30 cases, icterus was said to be present on the day of birth. As Gellis is careful to point out, hospital records were not used to confirm this point in Myers' series (or in the present report), but a sufficiently detailed history of accurate observation is rarely available. Klackenburg[21] has reported an infant with this disease whose father was a physician. No jaundice was noted until 6 weeks of age but the stools became acholic one week earlier. We have generally been unsuccessful in attempting to elicit an accurate history from parents on the onset of acholia in relation to definite jaundice and this point is only rarely mentioned in the literature. Fluctuations of the color of the stools due to staining with bilirubin-laden mucosal cells has been reported frequently, but we have been unable to estimate its true frequency. Such staining is considerably lighter in color than normal stools and the passage of dark feces after the onset of acholia casts grave doubt on the diagnosis of biliary atresia.

Another rare disease that can mimic the obstructive jaundice found in biliary atresia is cytomegalic inclusion disease. It has been our routine practice lately to examine a urine specimen for the presence of the characteristic inclusion bodies, but we have not yet found a jaundiced patient with this disease.

Another disease entity, where clinical separation ranges from difficult to impossible, has been variously labeled as the inspissated bile syndrome, neonatal hepatitis, or giant cell hepatitis. In our experience, this disease is more common than biliary atresia, in contrast to the experience of Hsia and co-workers[16] who found only 34 cases as compared to 94 cases of biliary atresia out of 156 cases of prolonged obstructive jaundice. At present, no

single laboratory determination or even a battery of such determinations appears to be of value in absolute separation of this disease entity from congenital biliary atresia.

The difficulty of diagnosis extends even to the operating table. Four of the present series were thought to be correctable at surgery and an anastomosis was attempted. Subsequent necropsy or surgical re-exploration showed complete biliary atresia. Lightwood and Bodian[26] reported a case in which anastomosis was similarly attempted and subsequent necropsy showed that the bile ducts had been patent and that the obstruction was due to a liver cirrhosis of obscure nature.

In one case of this series, no bile ducts were found at the time of laparotomy, but a bile-filled common bile duct was found at necropsy 7 months later. Kanof, Donovan, and Berner[17] report a case where exploratory laparotomy at 3 months failed to reveal a suitable duct for anastomosis. At necropsy, at 18 months, "a large gall bladder-like structure" was found that was 7 cm. in diameter and contained 35 c.c. of bile. This structure was connected to the intrahepatic ducts and would have allowed for surgical correction. They were able to find 14 similar cases in the literature. Leyva and Madigan[25] and Moore[31] each report a similar case, emphasizing the need for meticulous examination of the portal area at the time of laparotomy.

Laboratory Data.—Hsia and Gellis[15] have stated that the bilirubin values in biliary atresia steadily rise. Harris and colleagues[13] state that in biliary atresia the bilirubin either constantly rises or remains stable. Rapoport[34] states that the "jaundice increases progressively without remission" and that "inspissated bile of unknown etiology is suggested when serial determinations show a fluctuating bilirubin content instead of a progressively increasing one." In contrast, Christy and Boley[5] demonstrated a slight lowering of the average serum bilirubin values at about the third month. They attributed this to the small number of determinations made at this age in their series, but serial determinations in 6 of 16 infants showed either a decrease or a fluctuation over a period of 3 to 7 months. In a recent report, Hays[14] states that in 11 of 13 cases of neonatal hepatitis there was a definite decline during the study period, in contrast to 8 of 10 cases of biliary atresia where there was either no decline or a definite rise. Hays also found that the average total bilirubin content in patients with biliary atresia was higher than in children who ultimately proved to have neonatal hepatitis.

From analysis of the data in the present series, it is obvious that the scatter of total serum bilirubin values (Fig. 1) is such that an attempt to extrapolate any simple function would be unwarranted. Fig. 2 shows that serial bilirubin values in 6 cases fell only to rise or stabilize later. The key point of differentiating these patterns from those observed in the cases without atresia is a continuance of the decline to the point of virtual disappearance of jaundice. We agree with Hays that serial, usually weekly, determinations of serum bilirubin levels for at least 4 weeks is the single most valuable laboratory aid.

The thymol turbidity, cephalin-cholesterol flocculation, and total serum cholesterol values were not significantly different in biliary atresia. High levels of alkaline phosphatase, that is, over 20 Bodansky units or over 90 King-Armstrong units, were found only in cases of congenital biliary atresia. Seven of these high values occurred after 5 months of age, but this determination may be of some slight value in selecting cases for surgery if this observation is borne out by future analysis.

Mills and Mason[30] investigated the values of fecal urobilinogen in childhood with particular reference to the diagnosis of hemolytic anemias. The control group used included children with various liver diseases as well as normal children. The range in children under one year of age was 0.03 to 14 mg. of urobilinogen per day. In 4 infants with congenital biliary atresia, from 3 to 4 months of age, the values were all under 1 mg. per day. In the present series, only 4 values over 14 E.U./100 Gm. of feces were recorded in 2 cases without biliary atresia and only 7 values over 7 E.U./100 Gm., selecting the latter value since none of the cases with atresia had values over 6 E.U./100 Gm. This test again is of limited value in clinical diagnosis because of the low range of normal values in early infancy. Another drawback to this determination is that prior administration of antibiotics can reduce the excretion of urobilinogen in the feces.

The number of determinations of other liver function tests was too small to draw definite conclusions from but there appeared to be no obvious differences between the two groups. Fortunately, new liver function tests are being reported frequently, and it is hoped that one or more of these will prove to have lasting value in determining the presence of complete obstruction.

Survival.—In one case of the present series, only "fibrous cords" were found at laparotomy and a hopeless prognosis given to the family. The child gradually became less icteric and is in relatively good health at 16 years of age with a normal oral cholecystogram and what apparently is an intrahepatic biliary atresia. A number of similar spontaneous recoveries have been reported in the literature. Donovan[7] reported two cases, in one of which 2 children in the family had died of jaundice. Both children were in good health at 2½ years and 3 years after laparotomy. Large[24] reported a female infant who was found to have no ducts at laparotomy. There was no improvement for a month postoperatively, but the child subsequently improved and was normal at one year of age. Kanof[17] and Finlayson[8] each report a similar recovery. Gross[11] reports 3 babies who at operation were thought "to have only cord-like threads representing the ducts," but subsequently jaundice cleared and later they were in excellent health. Swenson and Fisher[42] and Rehbein and Neumann[35] also report having similar experiences in an undesignated number of their cases. Clatworthy and McDonald[6] observed 3 infants with "no extrahepatic bile ducts" at operation, two of whom subsequently cleared their jaundice while the third developed an external biliary fistula. Liver biopsies in these 3 cases were said to be consistent with neonatal hepatitis.

We emphatically disagree with the notion that the prognosis for the inoperable patient is uniformly hopeless. Indeed, there are now about one-fourth as many reports of recovery following a simple exploratory laparotomy as there have been following accepted corrective procedures.

SUMMARY AND CONCLUSIONS

A review of 30 cases of biliary atresia has been presented. None of these patients had a successful surgical anastomosis. The laboratory data of these cases and a group of 24 cases of prolonged obstructive jaundice due to other causes were analyzed. The difficulties of clinical and even surgical diagnosis were emphasized. Serial bilirubin determinations for 6 to 8 weeks would appear to offer the best laboratory aid. Levels of fecal urobilinogen in the high normal range are also of diagnostic value in excluding this disease but are rarely observed in infants.

One of the cases presented was found to have only fibrous cords at the time of surgical exploration and was given a hopeless prognosis. This child is still alive at 16 years of age and in relatively good health with what appears to be intrahepatic biliary atresia. A number of similar recoveries of "completely fibrotic biliary cords" have been reported in the literature. If at the time of initial exploration, no bile ducts of a size suitable for anastomosis can be found after operative cholangiograms and a thorough search, the best procedure is to do nothing further. The patient should be afforded the opportunity to see if there is any further capacity of the biliary system to grow and further operative intervention, such as hepatoenterostomy and attempts to produce internal biliary fistulas, left for a later date.

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CONGENITAL BILIARY ATRESIA

II. Analysis of the Therapeutic Problem

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As with any rare disease, review and summaries of case reports collected from the literature can offer a valuable supplement to the information that can be gleaned from the cases seen at any one institution. The first part of this report dealt with 30 cases seen at the University of Minnesota Hospitals.[45] The difficulty of clinical and even operative diagnosis was stressed. None of the cases seen at this center has been cured by surgical intervention, in contrast to cure rates as high as 50 per cent reported by others.[51] An accurate estimate of a cure rate, insofar as this can be determined, is of fundamental importance, for if surgical intervention can cure as many as half of these infants, then a few unnecessary early explorations of infants who prove not to have biliary atresia is justified. On the other hand, if our experience is nearer to the actual cure rate, then a more conservative period of watchful waiting until an accurate diagnosis can be reasonably well established should be the regimen of choice.

This in turn raises the question of the maximum period of time such a conservative approach is justified before irreversible liver damage results from prolonged biliary obstruction. Opinions offered by various authors range from advocating exploration at less than 4 weeks of age to at least 4 months of age.[11, 12, 19, 30, 33, 47, 83] (Grob[29] avoids this problem by stating, "Der Zeitpunkt der Operation ist gegeben, sobald die Diagnose gestellt ist.") None of these authors offer any data to justify these opinions except for isolated case reports.

A third problem is that of selection of operation, for again opinions, but little data, are offered.[29, 30, 43, 81] Does the operation that seems most physiologic necessarily offer the best prognosis or should the surgeon be guided by his own judgment as to what operation will be the easiest technically in each case? Finally, are operations that have been devised for use in adult patients with biliary obstruction suitable for use in infants?

In an attempt to answer these questions, case reports of congenital biliary atresia that have appeared in the literature in recent years were collected and analyzed. Since the last review of the literature was published in 1943,[15] 1945 seemed a proper year to start. The time period selected also had the advantage of including only those children who had been born and treated during the present antibiotic era and during a period when the important aspects of improved operative and postoperative management might be expected to offer the least number of variables.

Part of this investigation was carried out during the tenure of Postdoctoral Fellowship from the National Heart Institute, United States Public Health Service.

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MATERIALS AND METHODS

Articles pertaining to congenital biliary atresia that were listed in *Quarterly Cumulative Index Medicus* and *Current List of Medical Literature,* in the period from January, 1945, through May, 1959, were reviewed. A few references listed by the authors of these papers were found that had not been included in the original source references. All case reports of patients that were born after Jan. 1, 1945, are included in Tables I, II, and III. Sixty-nine cases from the United States and 53 cases from other countries are included in Table I; 15 cases of intrahepatic biliary atresia are listed separately in Table III.

The 30 cases seen at this center and reported in the first section are included under subsequent tables when appropriate, except for the patient in Case 18 who was born before Jan. 1, 1945.

All cases that were reported in sufficient detail to offer meaningful analysis were included. Essentially this eliminated only those cases in which general statements and summaries without clearly identifiable data pertaining to the individual cases were reported. In most instances it was possible to identify cases that were reported more than once and the duplications were eliminated; obviously a few duplications of which I am unaware may still be present. Finally, cases that were complicated by other lesions, such as a choledochal cyst or in which there was grave doubt as to the accuracy of diagnosis are included separately in Table II and were not further analyzed. In 7 cases the site of atresia was not stated but these cases were included in Table I and subsequently were analyzed.

RESULTS

Sex, Race, and Nationality.—Sex was stated in all except 39 instances. There were 56 females and 46 males. Sex did not affect the incidence of either theoretically correctable lesions or of successfully corrected lesions.

Race was reported in 55 instances of which 42 were Caucasian, 9 Negro, and 4 Oriental. These cases also were randomly distributed as to operability and outcome.

Cases were reported from all continents except Africa. It is probable that the disease is universally distributed but the number of cases is obviously insufficient to evaluate any possible regional trends.

Congenital Anomalies.—Twenty-two associated major congenital anomalies were described for 17 patients (Table IV). In the majority of cases there was no mention of associated anomalies so that this probably represents a minimum estimate. The incidence of anomalies in this report (11 per cent) shown in Table IV is in close agreement with the 16 per cent reported by Moore[57] and the 15 per cent reported by Myers.[62]

Congenital heart disease was reported 10 times for an incidence rate of 6.6 per cent or at least ten times that found in the general population.[23]

Antecedents.—In almost all of the cases, the pregnancy was considered to be uneventful. One mother had an illness similar to rubella and 3 infants were premature. Two cases occurred in one of a pair of twins. The case reported by Lebon was said to have occurred in one of identical twins, but the criteria

TABLE I. CASES OF EXTRAHEPATIC BILIARY ATRESIA REPORTED FROM 1945 TO 1959

CASE NUMBER	AUTHOR	RACE	SEX	JAUNDICE	AGE AT OPERATION	OBSTRUCTION	OPERATION	FOLLOW-UP	REMARKS
1	Bairov[2]	—	—	—	—	Hepatics	—	Died 4 mo.	Intestinal hemorrhage
2	Bairov[2]	—	—	—	2½ mo.	Complete	Exploratory laparotomy	Died 4 mo.	—
3	Bairov[2]	—	—	—	—	Common bile duct	—	Died 8 mo.	Bronchopneumonia
4	Bairov[2]	—	—	—	2 mo.	Complete	Exploratory laparotomy	Died 3½ mo.	—
5	Bairov[2]	—	—	—	2½ mo.	Common bile duct	Cholecystoduodenostomy	Well 7 mo.	—
6	Bancalari[3]	—	—	1½ mo.	4 mo.	Complete	Exploratory laparotomy	Died post-operatively	Bronchopneumonia
7	Bancalari[3]	—	—	5 wk.	—	Common bile duct and cystic	None	Died 1½ mo.	Autopsy only; hepatitis?
8	Blomstrand[4]	—	F	Birth	4 mo. 6 mo.	Complete	Exploratory laparotomy Hepatoenterostomy	Died 17 mo.	—
9	Bol. medico[34]	—	F	Birth	4 mo.	Complete	Exploratory laparotomy	Died 3 days post-operatively	Peritonitis, moderate cirrhosis present
10	Bol. medico[35]	—	F	—	—	Complete	None	Died 2 mo.	Bronchopneumonia, severe cirrhosis present
11	Bruton-1[5]	W	M	2 wk.	2½ mo.	Common bile duct	Cholecystoduodenostomy	Well 4 yr.	Syndactylism
12	Bruton-2[5]	—	M	—	2½ mo.	Common bile duct	Cholecystoduodenostomy	Well 3½ yr.	—
13	Bruton-3[5]	W	M	—	2½ mo.	Common bile duct	Cholecystoduodenostomy	Well 7½ mo.	Premature 4 lb., 12 oz.
14	Bruton-4[5]	W	F	—	5 mo.	Complete	Exploratory laparotomy	Died 19 mo.	—
15	Buxton[6]	N	M	Birth	4 mo.	Hepatics	External drainage	Alive 16 mo.	Still icteric
16	Chu[10]	O	M	1 mo.	5 mo.	Complete	Exploratory laparotomy	Died 10 days post-operatively	Bilateral inguinal hernias and ascites
17	Clatworthy[11]	—	—	—	3 mo.	—	Hepatoduodenostomy	"Cured"	—
18	Clatworthy[11]	—	—	—	5 mo.	—	Hepatoduodenostomy	—	Progressive biliary cirrhosis and liver failure

19	CC[12]	—	M	9 days	15 mo.	Complete	Exploratory laparotomy	Alive 17 mo.	Loud heart murmur
20	CPC[13]	—	F	6 wk.	—	Hepatics	None	Died 8 wk.	Acute duodenal ulcers and intracranial hemorrhages
21	Coste[14]	—	F	—	3½ mo.	Complete	Exploratory laparotomy	Died 1 day post-operatively	—
22	DeNicola[16]	—	—	Birth	1½ mo.	Common bile duct	Corrective procedure, type unstated	Well 8½ mo.	—
23	DeNicola[16]	—	—	—	—	Complete	None	Died 5 mo.	Autopsy only
24	Donato[18]	—	M	Birth	6 mo.	Complete	Exploratory laparotomy	—	—
25	Durrell[20]	—	M	Birth	3 mo.	Common bile duct	Cholecystogastrostomy	Well 4 yr.	—
26	El Mansoury[21]	—	F	15 days	4½ mo.	Common bile duct	Choledochoduodenostomy	Died 3 days post-operatively	Ascites on admission
27	Freeman[22]	—	F	1 mo.	3½ mo.	Complete	Exploratory laparotomy	—	—
28	Freeman[22]	—	F	"Recent"	2 mo.	Complete	Attempted hepatoenterostomy	Alive 10 mo.	Operation abandoned because of poor condition and no intrahepatic ducts seen grossly
29	Freeman[22]	—	M	—	2 mo.	Complete	Attempted hepatoenterostomy		No ducts seen grossly on sectioning the left lobe of the liver at operation, drained bile postoperatively
					6 mo.	Complete	Exploratory laparotomy	Died 12 hr. post-operatively	
30	Freeman[22]	—	M	3 wk.	5 mo.	Common bile duct	Choledochoduodenostomy	Well 6 mo.	—
31	Freeman[22]	—	F	Birth	2 mo.	Complete	Exploratory laparotomy	—	—
32	French[23]	N	F	Birth	7 wk.	Hepatics	Exploratory laparotomy	—	—
33	French[23]	N	F	7 wk.	—	Common bile duct	None	Died 2 mo.	Autopsy revealed theoretically correctable lesion

TABLE I—CONT'D

CASE NUMBER	AUTHOR	RACE	SEX	JAUNDICE	AGE AT OPERATION	OBSTRUCTION	OPERATION	FOLLOW-UP	REMARKS
34	Gray[26]	—	F	Birth	2 mo.	Common bile duct?	Cholecystogastrostomy	Well 1¼ yr.	Atretic site not demonstrated
35	Gray[26]	—	M	5 wk.	3 mo.	—	Cholecystogastrostomy	Well 1 mo.	Normal twin, premature
36	Hamilton[32]	N	M	6 wk.	7 wk.	Common bile duct	Choledochoduodenostomy	Well 18 mo.	—
37	Keller[38]	—	—	Birth	4 mo.	Common bile duct	Hepaticoduodenostomy	Well 18 mo.	Mild cirrhosis at surgery
38	Kirtley[39]	W	F	—	2½ mo. 3½ mo.	Fibrous cords Common hepatic	External drainage Hepaticoduodenostomy	Well 3½ yr.	—
39	Klackenburg[40]	—	F	6 wk.	—	Complete	None	Died 3 mo.	Intracranial hemorrhage, normal stools for first 5 wk.; autopsy only; mild cirrhosis
40	Knorre[41]	—	M	3-4 mo.	1¾ yr.	Complete	Exploratory laparotomy	Died 2½ yr.	Gastrointestinal hemorrhage
41	Knorre[41]	—	F	3 days	2½ mo.	Complete	Exploratory laparotomy	Died 8 mo.	—
42	Knorre[41]	—	F	Birth	7 mo.	Hepatics	Exploratory laparotomy	Died 1 day post-operatively	Bronchopneumonia
43	Koo[42]	O	M	3 wk.	6 mo.	Complete	Exploratory laparotomy	Died 1 day post-operatively	—
44	Koop[43]	W	M	Birth	6 wk.	Common bile duct	Hepaticoduodenostomy	Died "months later"	Imperforate anus
45	Koop[43]	W	F	Birth	6 mo.	Hepatics	External drainage	Died 12 days post-operatively	Liver failure and pneumonia
46	Koop[43]	W	M	2 days	1 mo.	Common bile duct	Cholecystojejunostomy	Well 2⅚ yr.	Maternal rubella?
47	Koop[43]	N	F	5 days	2 mo.	Common bile duct	Cholecystojejunostomy	Well 3 7/12 yr.	—
48	Larghero[48]	W	F	3 days	1½ mo.	Common bile duct	Cholecystogastrostomy	Well 7½ mo.	Cerebrovascular accident before surgery, but recovered

49	Larghero[48]	W	F	20 days	3 mo.	Complete	Exploratory laparotomy	Died 6 mo.	Severe cirrhosis at surgery; cachexia
50	Larghero[48]	W	M	2 days	6 mo.	Complete	Exploratory laparotomy	Died 9 mo.	Moderate cirrhosis at surgery; bilateral hydroceles
51	Lebon[49]	—	M	10 days	5½ mo.	Common bile duct	Choledochoduodenostomy	Died 2 days post-operatively	Normal, identical twin
52	Levin[50]	N	F	—	3 mo.	Complete	Exploratory laparotomy	Alive 3¼ yr.	Mild cirrhosis shown in biopsy at time of surgery
53	Levin[50]	N	F	Birth	4½ mo.	Complete	Exploratory laparotomy	Died 2⅙ yr.	—
54	McCarry[52]	—	M	—	12 days	Complete	Cholecystotomy and stab wound of liver	Died 7 mo.	Peritonitis following gastrojejunostomy; died 48 hr. post-operatively
55	McGeehan[53]	W	M	1 hr.	1 mo.	Complete	Exploratory laparotomy	Died 3 mo.	Also had erythroblastosis
56	Maingot[55]	—	M	2 wk.	1½ mo.	Common bile duct	Cholecystojejunostomy	Well 3 yr.	Subdural hematoma before surgery, but recovered
57	Mazza[56]	—	F	—	—	Complete	None	Died 2 mo.	Anomalies of mesenteric artery; died after transfusion accident; autopsy only
58	Moore-4[58]	—	—	—	6 mo.	Complete	Exploratory laparotomy	Died 12 mo.	Autopsy revealed dilated hepatic duct
59	Moore-5[58]	—	—	—	9 mo.	Common bile duct	Hepaticojejunostomy	Died 3 days post-operatively	Bronchopneumonia
60	Moore-6[58]	—	—	—	6 mo.	Common bile duct	Hepaticojejunostomy	Died 12 days post-operatively	Bronchopneumonia
61	Moore-7[58]	—	—	—	1 mo.	Common bile duct	Cholecystojejunostomy	Died 12 days post-operatively	Tetralogy, ileal stenosis, and right renal hypoplasia
62	Motsay-3[59]	—	—	7 days	6 wk.	Complete	Exploratory laparotomy	Died 10 mo.	—

TABLE I—CONT'D

CASE NUMBER	AUTHOR	RACE	SEX	JAUNDICE	AGE AT OPERATION	OBSTRUCTION	OPERATION	FOLLOW-UP	REMARKS
63	Motsay-6[59]	—	—	Birth	3 wk.	—	Cholecystoduodenostomy	Well 2 mo.	—
64	Motsay-7[59]	—	—	—	— 1 yr.	Complete Complete	Exploratory laparotomy Hepatoenterostomy	Died 1 yr. (postoperatively?)	—
65	Muzzo Pons[61]	—	—	Birth	—	Complete	None	Died 5 mo.	Autopsy only; bronchopneumonia
66	Muzzo Pons[61]	—	—	Birth	—	Common bile duct	None	Died 27 days	Bronchopneumonia
67	Muzzo Pons[61]	—	—	—	1 mo.	Common bile duct at ampulla	Cholecystoduodenostomy	Died 1 day postoperatively	Erythroblastosis and cerebrovascular accident
68	Muzzo Pons[61]	—	—	Birth	—	Common bile duct	None	Died 6 days	Autopsy only; chorioathetosis
69	Norris[63]	W	F	Birth	2½ mo.	Cystic duct	Hepaticoduodenostomy	Well 28 mo.	—
70	Notti[64]	W	F	6 days	6 mo.	Fibrous cords but "hepatic lake"	External drainage	Died 5 days postoperatively	No bile drained after surgery
71	Notti[64]	W	M	40 days	4 mo.	Fibrous cords	Exploratory laparotomy	Died postoperatively	Severe cirrhosis in biopsy at surgery
72	Notti[64]	W	M	2 mo.	5 mo.	Complete	Exploratory laparotomy	Died 4 hr. postoperatively	Malrotation of intestines; severe cirrhosis
73	Nutting[65]	W	F	2 days	—	Complete	None	Died 8 days	Anasarca and hypoproteinemia; severe cirrhotic changes already present
74	Paul[66]	—	—	2 mo.	3½ mo.	Common bile duct	Choledochoduodenostomy	Well 7 mo.	Erythroblastosis, but not exchanged; jaundiced at birth and edematous; faded at 2 wk.

75	Paul[66]	—	—	3 wk.	1½ mo.	Complete	Exploratory laparotomy	Died 11½ mo.	Erythroblastosis? (Anti-c, indirect Coombs weakly positive and not jaundiced early)
76	Redo-11[67]	W	M	6 mo.	7 mo.	Common bile duct	Cholecystoduodenostomy	Died 7 mo.	Massive rectal hemorrhage and died 4 days postoperatively
77	Redo-14[67]	W	F	6 days	31 days	Common bile duct	Exploratory laparotomy	Died 4 hr. postoperatively	—
78	Redo-15[67]	W	M	9 days	3 mo.	Complete	Exploratory laparotomy	Died 4 mo.	Multiple liver abscesses
79	Redo-16[67]	W	M	3 days	6 mo.	Complete	Hepatoenterostomy	Alive 5 yr.	Jaundice and hepatosplenomegaly
80	Redo-17[67]	W	F	5 wk.	7 wk.	Complete	Hepatoenterostomy	Alive 33 mo.	Jaundice and ascites
81	Redo-18[67]	W	F	Birth	6 wk.	Complete	Hepatoenterostomy	Alive 3½ mo.	Decrease in jaundice
82	Redo-19[67]	W	M	2 days	5 wk.	Complete	Exploratory laparotomy	Died 8 mo.	—
83	Redo-20[67]	O	F	3 mo.	11 mo.	Complete	Exploratory laparotomy	Died 13 mo.	—
84	Redo-21[67]	W	F	Birth	11 mo.	Complete	Exploratory laparotomy	Died 14 mo.	—
85	Redo-22[67]	W	F	1 mo.	—	Common bile duct	None	Died 7 mo.	Ascites and varices
86	Redo-24[67]	W	M	3 days	1½ yr.	Complete	Exploratory laparotomy	Died 1½ yr.	Ascites
87	Redo-25[67]	W	F	13 days	7 wk.	Hepatics	Hepatoenterostomy	Alive 4 mo.	Jaundiced, ascites
88	Redo-26[67]	W	M	3 days	24 days	Complete	Hepatoenterostomy	Alive 8 mo.	Occasional melena, jaundiced
89	Redo-27[67]	W	M	3 days	4½ yr.	Common bile duct	Attached ''small duct to intestine''	Alive 5½ yr.	Ascites, occasional melena, jaundiced
90	Rivarola[70]	—	M	—	1 mo.	Complete	Exploratory laparotomy	Alive 4 mo.	—
91	Rivarola[70]	—	F	—	6 mo.	Complete	Exploratory laparotomy	—	—
92	Rivarola[70]	—	F	—	6 mo.	Complete	Exploratory laparotomy	Died 11 mo.	—
93	Rivarola[70]	—	M	—	3 mo.	Complete	Exploratory laparotomy	—	—

TABLE I—CONT'D

CASE NUMBER	AUTHOR	RACE	SEX	JAUNDICE	AGE AT OPERATION	OBSTRUCTION	OPERATION	FOLLOW-UP	REMARKS
94	Rivarola[70]	—	F	—	4 mo. 6 mo.	Complete	Exploratory laparotomy External biliary fistula	Died 8 mo.	—
95	Rivarola[70]	—	F	—	2½ mo.	Complete	Hepatogastrostomy	Died 8½ mo.	—
96	Rivarola[70]	—	M	—	4 mo.	Complete	Hepatogastrostomy	Died post-operatively	Hemorrhagic diathesis
97	Rynecki[72]	—	M	2 days	2 mo.	Complete	Exploratory laparotomy	Died 4½ mo.	—
98	Rynecki[72]	—	F	3 days	2 mo.	Common bile duct	Cholecystoduodenostomy	Well 14 mo.	Common bile duct not enlarged
99	Sacrez[74]	—	F	Birth	1 mo.	Common bile duct filiform	Exploratory laparotomy	Died 1 yr.	Marked cirrhosis in biopsy at surgery
100	Sacrez[74]	—	F	2 days	2 mo.	Complete	Exploratory laparotomy	Died 4 days post-operatively	No autopsy
101	Sacrez[74]	—	F	3 wk.	2 mo.	Complete	Exploratory laparotomy	Died later	—
102	Sacrez[74]	—	M	—	2 mo.	Complete	External biliary fistula	Died 15 days post-operatively	Marked cirrhosis at autopsy
103	Sacrez[74]	—	M	—	5 mo.	Complete	Exploratory laparotomy	—	Moderate cirrhosis in biopsy at surgery
104	Schnug[76]	—	—	—	—	Hepatics	None	Died 4½ mo.	Pulmonary hemorrhage
105	Schnug[76]	—	—	—	1½ mo.	Complete?	Exploratory laparotomy	Alive 6½ mo.	Markedly jaundiced and portal hypertension
106	Schnug[76]	—	—	—	—	Distal common bile duct	None	Died 2 mo.	"Moderate to marked early cirrhosis"
107	Schnug[76]	—	—	—	6 mo.	Distal common bile duct	Cholecystoduodenostomy	Alive 1½ yr.	Still markedly jaundiced
108	Schnug[76]	—	—	—	—	Distal common bile duct	None	Died 1½ mo.	Moderate cirrhosis (labeled Case 7)

109	Schnug[76]	—	—	—	4 mo.	Complete	Exploratory laparotomy	Died	—
110	Schnug[76]	—	—	—	8 mo.	Complete	Exploratory laparotomy	Unknown	—
111	Schnug[76]	—	—	—	2 mo.	Complete	Exploratory laparotomy	Unknown	—
112	Schnug[76]	—	—	—	3 mo. 5 mo.	Complete Complete	Cholecystojejunostomy Hepatoenterostomy	Died after second operation	—
113	Schnug[76]	—	F	—	2 mo.	—	Cholecystoduodenostomy	Well 5½ yr.	Marked cirrhosis at 2 mo.; splenorenal shunt done at 3½ yr. because of portal hypertension
114	Sterling[78]	—	F	1 mo.	2 mo. 4 mo. 4 yr.	Hepatics	Exploratory laparotomy Hepatoenterostomy Southey tubes inserted	Died 4 yr.	Died 11 days following insertion of Southey tubes
115	Stiegler[79]	W	F	3 days	3 mo.	—	Cholecystogastrostomy	Well 1 yr.	Many postoperative complications
116	Stiegler[79]	W	M	—	7 wk.	Complete	Exploratory laparotomy	—	—
117	Strauss[80]	W	F	Birth	1½ mo. 5½ mo.	Hepatics	External drainage Hepaticoduodenostomy	Died 4 yr.	—
118	Vadheim[83]	W	M	Birth	3 mo.	Common bile duct	Hepaticoduodenostomy	Died 5 mo.	Severe cirrhosis at autopsy
119	Vadheim[83]	W	F	—	3 mo.	Complete	Exploratory laparotomy	Alive 5 mo.	—
120	Vernengo[84]	—	—	—	2 mo.	Common bile duct	Exploratory laparotomy	Died postoperatively	—
121	Weidenmann[85]	—	—	—	2 mo.	—	Cholecystoduodenostomy	Well 7 mo.	—
122	Whitten[86]	W	M	Birth	6½ mo.	Common bile duct	Cholecystoduodenostomy	Well 4¾ yr.	—

Under column labeled "race," W = white, N = Negro, and O = Oriental.

TABLE II. CASES NOT ANALYZED FURTHER

AUTHOR	RACE	SEX	ONSET OF JAUNDICE	AGE AT OPERATION	OBSTRUCTION	OPERATION	FOLLOW-UP	REMARKS
Grigorescu[28]	--	--	4 days	3 mo.	Complete	Hepatogastrostomy	Well 15 mo.	Direct bilirubin 72.5, indirect 69, extremely unlikely in congenital biliary atresia
Moore[57, 58]	W	M	6 hr.	1½ mo.	None demonstrated	Choledochotomy	Well 13 mo.	Erythroblastosis, recovered after simple probing of ducts
Motsay[59]	--	--	--	--	--	Cholecystoduodenostomy	--	Premature and cerebral spastic; insufficient information
Muzzo Pons[61]	--	--	40 days	2½ mo.	Common bile duct	Sectioned constricting band	Well 6½ yr.	Externally obstructed by band of connective tissue
Redo-12[67]	W	F	5½ wk.	10 wk. 4 mo.	Normal Complete	Exploratory laparotomy Exploratory laparotomy	Alive 6 yr.	Has brown stools and light urine
Redo-23[67]	W	M	1 yr.	5½ yr.	Common bile duct	Cholecystojejunostomy	Died 7½ yr.	Died 11 days after cholecystostomy, not counted, because of extremely late onset of jaundice
Ripstein[69]	--	F	Birth	4 mo.	Hepatics	Exploratory laparotomy	Died 2 wk. postoperatively	Peritonitis, associated choledochus cyst
Rosemond[71]	O	M	11 days	25 days	None demonstrated	Cholecystojejunostomy	Well 5 mo.	Common bile duct large but not examined for site of atresia, normal twin
Sacrez[74]	--	F	Birth	3 mo.	Bile ducts end in a choledochal cyst	Choledochogastrostomy	Died 5 days postoperatively	Marked cirrhosis at autopsy
Schumann[77]	--	M	5 wk.	3½ mo.	None demonstrated	Cholecystogastrostomy	Well 8 mo.	Gall bladder contained bile at surgery
Whitten[86]	--	M	5 days	1½ mo.	Common bile duct	Cholecystoduodenostomy	Well 1⅔ yr.	Inflammatory reaction around common bile duct, unlikely in congenital biliary atresia

TABLE III. CASES OF INTRAHEPATIC BILIARY ATRESIA REPORTED FROM 1945 THROUGH 1958

TABLE III. CASES OF INTRAHEPATIC BILIARY ATRESIA REPORTED FROM 1945 THROUGH 1958

AUTHOR	RACE	SEX	ONSET OF JAUNDICE	FOLLOW-UP	XANTHOMA	EXTRAHEPATICS	INTRAHEPATICS
Ahrens[1]	N	F	Birth	Died 3½ yr.	Yes—1¾ yr.	Left hepatic duct absent; others patent but small	No large or small ducts; plugs in canaliculi
Ahrens[1]	W	M	2 days	Alive 6½ yr.	Yes—3½ yr.	Hepatic ducts solid cords; others patent but small	No large or small ducts; plugs in canaliculi
Clinical Pathological Conference[13]	W	F	Birth	Alive 6 yr.	No—general brownish pigmentation	Normal	No bile ducts in portal areas; no bile stasis; slight widening of portal triad but no cirrhosis
Dobbs[17]	W	F	2 days	Died 2¾ yr.	Yes—20 mo.	Normal	No large or small ducts; plugs in canaliculi
Haas[31]	--	F	4 days	Alive 3⅝ yr.	Yes—3⅛ yr.	Common bile duct could not be identified with certainty at exploratory laparotomy at 16 days	Absent bile ducts; no cirrhosis and no bile stasis
Krahulik[44]	N	M	2 wk.	Died 9¼ yr.	No	Absence of entire tract	Rare intrahepatic bile ducts lined by low cuboidal epithelium; severe cirrhosis; hepatojejunostomy attempted at 6 mo.
MacMahon[54]	--	M	8 days	Living at 10 yr.	Yes—8 yr.	Normal	No interlobular bile ducts, but perilobular ducts were unduly conspicuous; minimal bile stasis and moderate degree of biliary cirrhosis
Moore[58]	--	M	--	Died 3 mo.	--	"Noncorrectable"	No bile ducts in any of 14 portal areas studied; no portal fibrosis or round cell infiltration
Moyson[60]	--	F	--	Living at 1 yr.	No	Normal	No major bile ducts and very rare secondary ducts; bile plugs in canaliculi
Notti[64]	W	F	2 mo.	Died 7 mo. (4 hr. postoperatively)	No	Absence of entire tract	No bile ducts seen; severe cirrhosis with increased peri- and interlobular fibrous tissue and abundant bile pigment
Redo[67]	W	F	Birth	Died 17½ mo.	--	Hepatic, common and cystic ducts absent	"No intrahepatic duct tissue on autopsy"
Sacrez[73] (1946)	--	F	8 days	Died 3⅓ yr.	No	Normal	No ducts in 90 out of 100 portal spaces
Sacrez[74] (1956)	--	M	2 mo.	Died 3 mo.	--	Normal, but narrow	Rare bile ducts in portal spaces; minimal cirrhosis but intense bile stasis
Sass-Kortsak[75]	--	F	3 days	Died 3½ mo.	--	Normal	No bile ducts in 495 of 500 portal tracts; very little bile stasis; moderate increase in fibrous tissue in portal tracts but no inflammatory cells
Swenson[81]	W	M	--	Alive 11 yr.	--	--	--

TABLE IV. INCIDENCE OF ASSOCIATED MAJOR CONGENITAL ANOMALIES

Cardiovascular malformations	13	
Ventricular septal defect		4
Total anomalous pulmonary return		1
Tetralogy of Fallot		1
Idiopathic hypertrophy of right ventricle		1
Congenital heart disease, incompletely diagnosed		3
Anomalous position of mesenteric artery		1
Trifurcation of pulmonary artery		1
Aberrant right subclavian artery		1
Gastrointestinal malformations	5	
Imperforate anus		3
Ileal stenosis		1
Malrotation of intestines		1
Miscellaneous	4	
Unilateral renal hypoplasia		1
Polycystic kidneys		1
Syndactyly		1
Bilateral equinovarus		1

Cases of inguinal or umbilical hernias or hydroceles are not included.

for determining that these were indeed monovular twins are not stated. Three definite cases and one probable case of associated erythroblastosis fetalis were reported.

Length of Survival and Causes of Death.—The median age of death in the inoperable and unoperated cases was approximately 5 months (Table V). It is interesting to note that this is not significantly different from that reported by Holmes[36] in 1916.

TABLE V. LENGTH OF SURVIVAL OF INOPERABLE OR UNOPERATED CASES

AGE	DEAD	ALIVE
Under 1 month	3	
1-3 months	11	1
4-6 months	18	3
7-9 months	9	1
10-12 months	4	1
13-15 months	4	1
16-18 months	1	2
19-21 months	2	
22-24 months		
2 years	2	1
3 years	1	1
4 years	2	
5 years		1
Total	57	12

Cases of associated intrahepatic biliary atresia are not included in this table.

A total of 66 causes of death were found for 50 patients (Table VI). The leading causative factor appears to be operation, 25 patients having succumbed in the immediate postoperative period. Other important causes of death were diseases of the respiratory tract (13 cases), liver damage (11 cases), hemorrhagic phenomena (11 cases), and peritonitis (3 cases). Hemorrhagic phenomena of less than fatal degree were also frequently reported, and 3 infants were reported to have survived intracranial hemorrhages.

Intrahepatic Biliary Atresia.—The cases of intrahepatic biliary atresia are listed separately in Table III for convenience. Among the cases of extrahepatic biliary atresia listed in Table I, information concerning the status of the intrahepatic biliary tree was definitely stated in a minority of the published reports. In all likelihood, several cases with associated intrahepatic biliary atresia are included in these tables. This factor, plus the small number of proved cases of intrahepatic biliary atresia, speaks for the need for great caution in drawing conclusions from this table.

Two statements in regard to intrahepatic biliary atresia are probably justified in spite of these objections. First, the survival in this group of cases is longer than the 5-month median for isolated extrahepatic biliary atresia. Second, the degree of cirrhosis present would also appear to be less than in those cases not accompanied by intrahepatic biliary atresia.[46]

TABLE VI. STATED CAUSES OF DEATH

Postoperative deaths	25	
Liver damage	11	
Ascites		5
Esophageal varices		1
Liver failure		2
Anasarca		1
Pericardial effusion		1
Multiple liver abscesses		1
Respiratory tract	13	
Bronchopneumonia		10
Aspiration pneumonia		1
Acute purulent bronchitis		1
Atelectasis of lungs		1
Hemorrhagic phenomena	11	
Intra-abdominal hemorrhages		3
Gastrointestinal hemorrhages		3
Central nervous system hemorrhages		3
Pulmonary hemorrhage		1
Generalized		1
Miscellaneous	6	
Peritonitis		3
Prematurity		1
Acute ulcerative colitis		1
Transfusion accident		1

DISCUSSION

The individual case reports in the literature are heavily biased by a natural tendency to report operative cures and not to report the more common inoperable or unsuccessful cases. Thus, of the cases in Table I, 21 per cent were successfully corrected and an additional 17 per cent had lesions that were theoretically amenable to surgery but where either operation was not performed or had failed. Eleven of the cases reported were considered by the author not to have biliary atresia and have been excluded from the final tabulation. Several others must be considered as presumptive only, since the site of atresia was not reported.

A more reliable estimate of correctability may be obtained by restricting consideration to only the larger series reported. Holmes'[36] classic report, in which he analyzed 114 cases reported in the literature prior to 1916, concluded that 16 per cent of these cases were theoretically repairable.* Table VII lists the more recent series, composed of 10 or more cases of biliary atresia.

Donovan[19] reported 18 cases of congenital atresia with one operative success and one case, found to be correctable at autopsy, which had been thought to be inoperable at the time of a previous exploratory laparotomy. Two of the cases included were thought to have complete biliary atresia at repair, but subsequently cleared their jaundice. Six of the other cases were clinical diagnoses only, and have been eliminated from the corrected figures. The series reported by Leyva and Madigan is the most optimistic reported to date. The only available information on this series is a brief note summarizing an exhibit at a medical meeting. This report refers both to 18 and 19 patients as the correct total.

TABLE VII. INCIDENCE OF SURGICAL CORRECTABILITY, AS REPORTED IN SERIES OF 10 CASES OR MORE

AUTHOR	YEAR	CASES	THEORETICALLY CORRECTABLE	PER CENT	SUCCESSFULLY CORRECTED	PER CENT
Donovan[19]	1937	18	2	11	1	6
		(10)*	(1)	(10)	(1)	(10)
Leyva[51]	1948	18	9	50	5	28
Gerrish[25]	1951	25	1	4	1†	4
Moore[58]	1952	31	8	26	1	3
		(30)	(7)	(23)	(0)	(0)
Gross[30]	1953	146	27	18	12	8
Koop[43]	1954	39	4	10	2	5
Redo[67]	1954	27	10	37	2	7
		(25)	(9)	(32)	(1)	(4)
Greaney[27]	1954	21	9	43	3	14
Kirtley[39]	1954	10	1	10	1	10
Myers[62]	1956	40	9	22	4	10
Clatworthy[11]	1956	16	2	12	1	6
Rehbein[68]	1957	14	2	14	2	14
Grob[29]	1957	20	--	--	3	15
Schnug[76]	1958	10	5	50	1	10
Christy[9]	1958	37	--	--	4	11
Krovetz[46]	1959	30	2	7	0	0
Total		503	91	20.2	43	8.5
Corrected total		491	88	20.3	41	8.1

*The figures in brackets eliminate the doubtful cases in the series reported in the line immediately above. See text and Table II for details. Corrected totals calculated after elimination of these cases.

†Report states that "the extrahepatic biliary ducts could be anastomosed" but not whether this was done successfully or not.

-- Data not clearly separable and report not included for calculations.

One of Moore's[58] cases and two of Redo's[67] cases are not considered by the author to have had biliary atresia and are listed separately in Table II. As may be seen from Table VII, only 8 per cent of these patients have actually been cured. As far as I have been able to determine, there have been a total of only 65 surgical cures reported in the medical literature through May, 1959.

*Careful review of his illustrations and reports indicates that 9 of these cases had no obstruction to the flow of bile per se, that three were choledochal cysts and not biliary atresia, and that 10 others were considered doubtful cases. Eliminating these cases changes the estimate of theoretical correctability to 23 per cent.

Timing of Operation.—A variety of opinions exist as to the optimal time for surgical exploration. Gross[30] states that "if one delays in making a positive diagnosis of congenital biliary obstruction until the infant is 4 to 6 weeks of age, the chance of (diagnostic) error is not great. Generally it is better not to operate upon patients with biliary obstruction before the end of the first month. Nothing is lost by this delay, and the assurance of a more accurate diagnosis is gained." Koop[43] feels that surgery is justified "as soon as a diagnosis of obstructive jaundice is established." In an editorial written in 1948, Lanman[47] recommended operation between 4 and 5 weeks of age. Moore,[58] citing Lanman, states that "perhaps they should be operated on even soonor . . . than four or five weeks of age." In contrast, Harris, Andersen, and Day[33] prefer to delay exploration until the age of 4 months. Wooley[12] bases a diagnosis of congenital biliary atresia on progressive jaundice of at least 3 months' duration and increasing hepatomegaly.

Theoretically, at least, if delaying surgery to the age of 4 to 6 weeks eliminates part of the diagnostic error, further delay might eliminate other sources of error and thus, unnecessary operation. This is particularly true for those patients with cases due to neonatal hepatitis or to small fibrous-appearing ducts in whom the jaundice relents spontaneously. Unfortunately, not enough information was recorded in the surveyed literature to arrive at an estimate of the delay needed for this latter phenomenon to occur.

From data reported in the first part of this report, at least 2 to 3 months is needed to exclude jaundice not due to biliary atresia. Gellis, Craig, and Hsia,[24] in discussing neonatal hepatitis, state: "It is of importance to note that the morbidity and mortality was limited almost entirely to the group which had undergone surgical exploration. . . . (This) could not be explained by the presence of more severe disease." Newer anesthetic agents and the use of operative cholangiography as advocated by Swenson and Fisher[82] would seem to have made exploration for biliary atresia a more benign process than it has been in the past.

Early, and in fact nearly immediate, exploration is urged by Clatworthy and McDonald[11] who also have been using limited exploration, operative cholangiograms, and liver biopsies. Seven cases of neonatal hepatitis were explored using this technique. Four of the 7 died, 2 had cirrhosis and postal hypertension when last seen at 4 and 6 years of age, and one was lost to follow-up. Greaney[27] found 11 of the patients subjected to exploratory laparotomy to have normal extrahepatic ducts. Of these 11, 7 died, 3 were living and well, and one was not followed. I do not understand how Greaney can then conclude, "If one does explore these infants and backs away after demonstrating a normal extrahepatic biliary system by cholangiography, one doesn't subject the child with hepatitis or sepsis to very much of a procedure. Most of the patients tolerate it well." Furthermore, this procedure would not uncover atretic segments or segments suitable for anastomosis high in the portal hilus and a thorough exploration of the hilus should be done if dye does not pass into the duodenum. The use of operative cholangiography, or variants of this using saline

or methylene blue with direct observation has resulted in several false negative examinations and should be interpreted with caution.

Another factor to consider in the timing of surgical intervention is the development of biliary cirrhosis, in the event of excessive delay, which might negate a successful surgical anastomosis. Myers[62] found some degree of cirrhosis in 18 of 21 biopsy specimens examined. The 3 patients without cirrhosis were 3 months, 3 months, and 5 months of age, respectively, while 7 cases of cirrhosis occurred in children under 5 months of age. Christy and Boley[9] determined the amount of fibrous tissue in 31 specimens of liver tissue obtained from 27 patients with congenital biliary atresia. They were able to show "a great variability in the amount of fibrosis that may be present at any specific age." Only 3 patients were considered to have normal liver architecture. These patients were 1 month, 2 months, and 4 months of age. One patient had mild fibrotic changes at approximately one year of age, while 2 patients had severe fibrosis when under 3 months of age. Thus, while there was generally a progression of fibrosis with age, the relationship was not a linear one. Only a limited analysis of this point could be made from the case reports, but evaluation of the degree of cirrhosis in the cases in the present series similarly shows no clear-cut correlation with age. To further complicate the relationship of cirrhosis to successful outcome of a case is the extraordinary regenerative power of the liver. Theoretically at least, this might overcome a moderate amount of cirrhosis that was already present at the time of operation.

In an attempt to elucidate the relationship of successful surgical outcome to the timing of operation, all 43 patients who had an operable lesion and on whom curative procedures were done were analyzed. In 3 instances the age at operation was not given in the original report. Analysis of both the successes and failures by age at the time of operative intervention is shown in Table VIII. There appears to be little difference in the prognostic implication of age until after 4 months of age, and recovery has occurred following anastomoses at 5, 6, and 8[37] months of age.

TABLE VIII. CORRELATION OF AGE OF SURGERY AND SURGICAL SUCCESS IN THOSE CASES THAT WERE THEORETICALLY CORRECTABLE AND HAD CORRECTIVE SURGERY

AGE OF SURGERY	SUCCESSES	FAILURES
Under 1 month	2	1
1st month	5	4
2nd month	9	1
3rd month	6	1
4th month	1	2
5th month	1	1
6th month and over	1	5
Unknown*	0	2
Totals	25	18

*Unknown time and unknown result in one additional case not listed.

Choice of Operative Repair.—Gross[30] states "If some patent duct is available (which joins with the liver), it is much better, as a general rule, to anastomose the hepatic or common duct, rather than the gall bladder, to the duodenum, in spite of the fact that the latter is technically easier to accomplish."

The former method more nearly duplicates the normal anatomic biliary flow. Among the 60 attempts at a corrective operative procedure listed in Table IX, there are 34 in which the ducts were used for anastomosis and 26 in which the gall bladder was employed. From the data in this table, there would appear to be no significant correlation between the type of surgical procedure and operative success. There were no obvious differences in postoperative morbidity or complications in the reports following various types of anastomoses.

TABLE IX. CORRELATION OF TYPE OF OPERATION AND SURGICAL SUCCESS

	SURVIVING AND IN GOOD HEALTH	DIED OF VARIOUS CAUSES OR IN POOR HEALTH
Choledochoduodenostomy	9	7
Cholecystoduodenostomy	11	5
Cholecystogastrostomy	4	0
Cholecystojejunostomy	4	2
Hepaticoduodenostomy	8	10
Total	36	24
Hepatoenterostomy	0	17†
Not stated	1	1
External drainage	1*	6
Cholecystotomy	0	2

Includes 31 cases in Gross' text.[30]
*Hepaticoduodenostomy done 1 month later and also listed as such.
†One also had Southey tubes inserted without success.

A commonly recurring and often subtly implied idea is that the surgical diagnosis of inoperability is accurately and easily established at laparotomy. As noted in the first section of this report, about one-fourth as many patients have recovered following a simple laparotomy when a diagnosis of complete atresia of the biliary tract was considered established, as have been cured following accepted corrective procedures. Hamilton[32] expresses a commonly held attitude, "any procedure that may be indicated on exploration will be justified, since all these cases are fatal without corrective maneuvers." Dahl-Iversen and Gormsen[15] imply the same thing when they state that an attempt to anastomose the liver to the intestinal tract (hepatoenterostomy) is justified if no biliary ducts suitable for anastomosis can be found. This opinion is offered in spite of the fact that they were unable to find any report of favorable results following hepatoenterostomy. In the present series, 17 hepatoenterostomies (insertion of cut surface of liver in an opening in the bowel) are presented without a single surgical success. In the few cases reported in which the patients were autopsied some months after a hepatoenterostomy, the junctional hepatic-enteric tissue was heavily fibrosed and obviously not functional. This operation appears to be without merit in congenital biliary atresia, in which the intrahepatic biliary ducts are exceedingly small.[30] Even less of merit can be said for attempts to create internal biliary fistulas by incising the liver or inserting Vitallium tubes.

SUMMARY AND CONCLUSIONS

One hundred and thirty-seven reported cases of patients with congenital biliary atresia born after Jan. 1, 1945, are reviewed. Of these, 15 were of the

intrahepatic variety and 76 lacked extrahepatic ducts of a nature amenable to curative surgery. A critical review of reported series and our own cases reveals that only 19 per cent of these cases offer ducts theoretically suitable for operation. The number of cases actually cured by operation is discouragingly small, a total of only 65 cures having been reported to date. Analysis of the reported series, after eliminating cases that probably did not have congenital biliary atresia, results in a cure rate of 8 per cent.

As mentioned in the first part of this report, at least 14 cases that were thought to be inoperable and given a hopeless prognosis, but who subsequently cleared their jaundice, have now been reported. Among the surgical cures reported, details as to the site of atresia and the presence of dilatation above the atretic site were frequently not reported. I believe that several of these so-called cures might also have had a spontaneous relief of jaundice or might actually have been cases of neonatal hepatitis.

Theoretically, the operation of choice would be the one which most nearly duplicates the normal anatomic biliary flow. However, from the data reported, there does not seem to be any obvious operation of choice in terms of operative success.

I was unable to find a single surgical success following hepatoenterostomy, external or internal drainage of bile. Since operative diagnosis is not infallible, the procedure of choice if no correctable atresia can be found, would seem to be not to attempt these procedures at initial exploration. Spontaneous remission of the jaundice or growth of a small duct that did not appear suitable for anastomosis at the time of initial exploration have occurred at later dates and offer more hope than these singularly unsuccessful operations. Unfortunately, no estimate of the time needed for these phenomena to occur can be made from the available literature.

A variety of opinion exists as to the optimal timing of surgical intervention, ranging from less than 4 weeks to more than 4 months. While there is generally a progression of fibrotic changes with age, cases have been reported with severe fibrosis at early ages and other cases with little or no fibrosis at later ages. Analysis of 40 cases in which curative procedures were done and the ages at operation were stated shows relatively little prognostic implication with age until after 4 months of age. Some degree of caution is needed before drawing firm conclusions from these data because of the small numbers involved in the individual age categories. From analysis of the data available pertaining to diagnosis and operative success, conservative watchful management for at least 4 weeks or until the patient is approximately 3 months of age would seem to be the best policy at present.

I wish to express my gratitude to Dr. L. K. Pickett, Department of Surgery, State University of New York, Upstate Medical Center, who first aroused my interest in this disease and to Dr. William Krivit, Department of Pediatrics, University of Minnesota, who contributed many valuable suggestions for the analysis and organization of the data.

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CONGENITAL DIAPHRAGMATIC OBSTRUCTION OF THE DUODENUM

Report of an Unusual Case in a Child

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CONGENITAL intrinsic duodenal obstruction in its many varieties is a rather unusual condition. The classification of these duodenal malformations proposed by Forssner[3] follows:

1. Diaphragm
   a. Complete or imperforate
   b. Incomplete or perforate
2. Stenosis
3. Atresia
   a. Blind ends connected by a band
   b. Blind ends unconnected

The least common among these various types is the duodenal diaphragm. Madden and McCann[5] were able to collect 86 cases of complete or incomplete duodenal diaphragms from the literature to January, 1955, and they added 3 cases of their own. Since then, there have been various isolated reports of 1 to 4 cases[1, 2, 4] in the English literature. The following case is reported to emphasize an important surgical aspect of the operation on these patients.

CASE REPORT

A 5-year-old girl was first seen at the Mayo Clinic on May 19, 1954, because of repeated vomiting since birth. Episodes of vomiting began in the neonatal period and had occurred as often as every 2 weeks since then. The vomitus consisted of foods taken during the previous two or three feedings. The child appeared normal and was symptomless between bouts of vomiting. Development was considered to be normal by the parents when compared to that of other siblings, although gain in weight was slow. At the age of 20 months, the patient had a severe attack of vomiting preceded by marked abdominal distention. At that time she had required hospitalization and administration of fluid and electrolytes parenterally. Subsequently, intermittent mild attacks of vomiting continued and occurred about once a month.

The child, at the age of 5 years, was 41½ inches tall and weighed 36¼ pounds. Physical examination was essentially negative. Roentgenologic examination of the stomach and duodenum with barium sulfate showed such immense dilatation of the first and second portions of the duodenum that the capacity appeared greater than that of the stomach (Fig. 1). Roentgenograms of the colon indicated that the cecum lay in approximately normal position. It was obvious that the child must have partial obstruction in the distal part of the duodenum. Diagnoses entertained included incomplete rotation of the midgut with obstruction of the duodenum by peritoneal band, congenital stenosis of the duodenum, and annular pancreas.

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On May 24, 1954, operation was carried out, and incomplete rotation of the midgut was found. The liver and gall bladder were normal. Both kidneys were present and felt normal. There was no Meckel's diverticulum. The mesentery of the right part of the colon had not fused to the body wall, but it was long enough so that the cecum appeared in the right lower quadrant of the abdomen on x-ray examination prior to operation. The cecum could be displaced into the left side of the abdomen as well. The mesentery of the small intestine had not fused to the body wall posteriorly. The stomach was thick-walled and enlarged, and the first and second portions of the duodenum were as large as the stomach. The remainder of the small bowel appeared normal in size. Adhesive bands attached the right side of the colon to the body wall posteriorly and appeared to compress the duodenum at its point of narrowing. After those had been divided one could see that the duodenum joined the jejunum without any ligament of Treitz and that the superior mesenteric vessels did not cross the duodenum. Thus the child had incomplete rotation of the midgut. It appeared that division of the peritoneal band would relieve the duodenal obstruction, but in an effort to exclude intrinsic obstruction a small opening was made in the jejunum below the point of obstruction and a finger was passed through the point of previous obstruction. No intrinsic lesion, such as diaphragm, could be palpated. The patient withstood the operation nicely and had a smooth convalescence. She was dismissed from the hospital on the tenth postoperative day. On dismissal, she was free from discomfort.

Fig. 1.—May 21, 1954, before the first operation. The stomach and upper part of the duodenum are greatly dilated.

The patient returned 6 months later for re-examination. Since the operation she had vomited briefly only twice and had been able to retain various solid foods which she had not been able to eat previously. Her parents considered the operation a complete success. However, roentgenologic examination of the stomach showed that the stomach and first and second portions of the duodenum were still dilated with retained food and secretion. There was still obstruction at the junction of the second and third portions of the duodenum with ineffective hyperperistalsis in the duodenum. The x-ray picture appeared much as it had preoperatively. Inasmuch as the child had no symptoms, no further operation was advised. Her mother was instructed to notify us immediately should symptoms appear.

The child returned on Aug. 28, 1956, 27 months after operation. She had continued to fare well without symptoms. She had vomited perhaps twice since the previous examination, weighed 46 pounds, and measured 47 inches in height. Roentgenograms of the stomach and duodenum (Fig. 2) still showed an abrupt, bandlike constriction of the duodenum at the junction of its descending and transverse portions with secondary dilatation of the stomach and duodenum above the constriction. Again her mother was advised to continue as before but to bring the child back for duodenojejunostomy should vomiting and retention recur.

On Oct. 27, 1956, vomiting recurred and was persistent. After correction of fluid and electrolyte imbalance, a second operation was performed. The patient, of course, still had incomplete rotation of the midgut with a mobile cecum and no fusion of the mesentery of the small intestine to the body wall. The huge upper portion of duodenum narrowed abruptly. Preparations were made to perform side-to-side duodenojejunostomy. When the duodenum was opened, a mucosal septum was found. A hole no more than 4 mm. in diameter pierced the diaphragm eccentrically. It was obvious that this diaphragm had been the principal cause of obstruction all along. In the light of this finding it was hard to believe that the child could have had as few symptoms as she did. The bile duct and pancreatic duct could not be found in the diaphragm. The septum was excised, and the resulting defects in the interior of the duodenum were closed with a continuous running stitch of chromic catgut. The side-to-side duodenojejunostomy was subsequently completed.

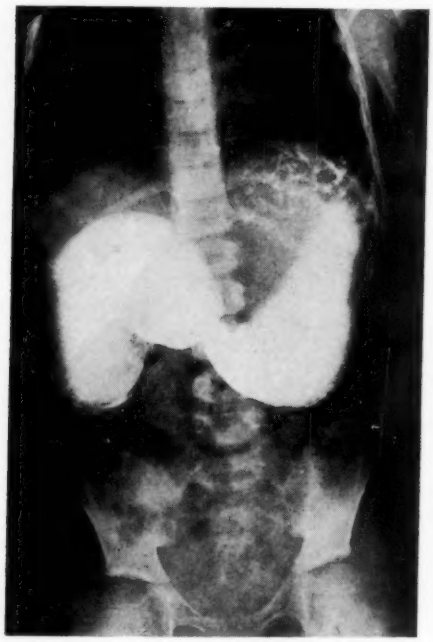

Fig. 2.

Fig. 3.

Fig. 2.—Aug. 28, 1956, after the first operation. Again the stomach and upper part of the duodenum are hugely dilated, although the patient had improved clinically.

Fig. 3.—Jan. 1, 1957, after the second operation when the diaphragm was located and excised. The upper part of the duodenum is reduced in size and there is no impediment to the flow of barium distally to the rest of the gut. (Courtesy of Dr. J. F. Edwards, Clinton, Iowa.)

The patient's convalescence was smooth, and she was dismissed 11 days after the operation. Since then she has done well. Roentgenologic examination in her home locality in January, 1957, showed that the size of the first and second portions of the duodenum had diminished and that barium passed promptly into the jejunum (Fig. 3).

The last correspondence from her mother, dated July 31, 1959, indicated that the patient was well.

COMMENT

The cause of congenital intrinsic obstruction of the duodenum, particularly diaphragmatic occlusion, is still unknown. Diaphragmatic lesions of the duodenum seem to be equally frequent in the two sexes. The complete or imperforate form gives rise to symptoms immediately after birth, as does any other completely obstructive lesion of the intestine. The perforate diaphragm usually gives rise to intermittent obstruction starting shortly after birth, although at times the condition may be encountered as an incidental finding at necropsy on adults if the opening in the diaphragm is large.

Duodenal diaphragms usually have occurred in the second portion of the duodenum near the level of the ampulla of Vater. Both the common bile duct and the pancreatic duct have been reported to traverse the diaphragm, and either or both ducts may empty into the bowel from either surface of the diaphragm.[8] In carrying out surgical excision of the diaphragm this fact must be borne in mind if accidental division and occlusion of these ducts is to be avoided. Less frequently, in 16 per cent of cases,[5] the diaphragm is located just above the ampulla. The vomitus in such patients will contain no bile.

The apertures in the perforate type of diaphragm are located eccentrically in the majority of instances recorded. Their sizes vary from 1 to 10 mm.; this explains why some patients present symptoms of severe obstruction, but others do not. Although the simultaneous occurrence of diaphragmatic obstruction of the duodenum and extrinsic obstruction of the duodenum associated with incomplete rotation of the midgut is uncommon, it apparently happens often enough to warrant being kept in mind during operations for the latter condition. One of the three patients with duodenal diaphragm whose cases were reported by Madden and McCann had associated malrotation. Since then, in 2 of the 7 cases that have appeared in the English literature,[1, 2, 4] including ours, malrotation was associated. St. John and Tamoney[9] reported a rare case of duodenal septum associated with annular pancreas in which the annular pancreas played no role in the obstruction at all.

It is easy to understand how these patients can be subjected to multiple operations before the existence of the diaphragm is recognized and the obstruction relieved, when the surgeon has corrected the extrinsic anomaly first and has assumed it was the only source of obstruction present. The purpose of this report is to call attention again to this pitfall and to suggest a means of prevention.

These diaphragms are fairly thin, being only 0.5 to 4.0 mm. thick. They are composed of two layers of duodenal mucosa placed back to back with a thin layer of submucosa between. It is ordinarily impossible to feel them through the intestinal wall. Their detection demands (1) knowledge that they may be present despite the presence of other anomalies, and (2) adequate examination of the patency of the duodenum. It is said that a constricting ring can sometimes be detected in the duodenum at the level of the diaphragm[5, 8]; we did not notice such a ring in our case, although we must admit we did not seek it. Ferguson and Rothfield[2] have stated that when the transition between hypertrophied dilated duodenum and normal intestine distal to it is *abrupt,* the obstruction is usually not due to purely extrinsic causes.

The problem is how best to examine the lumen of the duodenum for patency. In our case, digital palpation through an enterotomy failed, presumably because the soft diaphragm retreated in advance of the finger and because the finger was not inserted far enough to exceed the elasticity of the membrane. If a small catheter were used in place of the finger, it might pass through a small opening in the diaphragm and falsely indicate absence of obstruction. Passage of a Foley catheter with its balloon inflated to the diameter of the normal distal duodenum should detect any diaphragm that might be present if care is taken to move the catheter completely through the area in question. We plan to use this technique or some variant of it in future cases. Such a catheter, or in larger individuals, a Miller-Abbott tube, could be passed into the duodenum via the esophagus and stomach to avoid enterotomy.

The operation of choice for duodenal diaphragm, provided bile and pancreatic ducts are not compromised, is duodenotomy and incision of the diaphragm as devised by Morton.[6, 7] Short-circuiting procedures such as duodenoduodenostomy or duodenojejunostomy are often applicable and have been employed by different surgeons with good results.

SUMMARY

Duodenal diaphragm is a rare anomaly causing obstruction of the duodenum. Due to the fairly frequent accompaniment of other extrinsic causes of duodenal obstruction, particularly malrotation of the intestine, this intrinsic lesion may be missed during an operation, necessitating a second operation before the malformation is finally corrected. Detection of these diaphragms requires (1) knowledge that they may be present with or without the presence of other anomalies and (2) accurate determination of the patency of the duodenal lumen. Even when the lesion is suspected, it may not be detected by digital examination through a duodenotomy. We have suggested that a small Foley catheter or, in larger patients, a Miller-Abbott tube can be used to explore the lumen of the duodenum.

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Editorials

Conducted by I. S. Ravdin, M.D., and J. Garrott Allen, M.D.

Microscopic Diagnosis of Carcinoma of the Lung

Whenever possible, a microscopic diagnosis should be established before a surgical procedure is undertaken for attempted cure or palliation of carcinoma of the lung. There is no adequate substitute for a bronchoscopic biopsy if the lesion is within the reach of the bronchoscope. However, when an unidentified mass is not approachable by other means, an exploratory operation may be indicated. A supraclavicular lymph node biopsy, if positive, rings down the curtain on any attempt at curative surgical procedure.

Carcinoma of the lung originates, as now known, from epithelial cells lining the bronchial tree. The usual sites, in decreasing frequency, are, first, in the bronchi themselves, second, where the bronchi branch to the lobes, and, third, where the branches twig to lobules. About one-half of the carcinomas of the lung occur at sites within the range of the bronchoscope and are usually amenable to biopsy. When the growth originates in the branches of the bronchial tree past the limits of bronchoscopic view, cells that shed from the ulcerated surface into the lumen may be carried in the secretions and they may appear in bronchial washings and may be demonstrated on smears. Coughed-up sputum rarely yields positive results in cytologic diagnosis and is therefore not routinely used.

Shedding of the cells does not occur until the surface epithelium has been interrupted by neoplastic cells resulting in ulceration. The most vicious property of the epithelial cancer cells is their loss of coherence or their "stickingness" to one another. In contrast to the manner in which the normal epithelium covers a denuded surface, epithelial cancer cells fray, "duck" below the surface, and tend to flee from their companion cells, multiplying on the way. Their separation from one another apparently results in change of shape of the cells and in their loss of polarity. The presence of the epithelial cancer cells stimulates proliferation of the nearby connective tissue cells and of the endothelial cells. These provide the stroma for the multiplying cancer cells.

By the time ulceration occurs, the growth has expanded to varying depths through the wall of the bronchus and even into the adjacent lung tissue. Neoplastic cells have already penetrated into tissue spaces, lymph spaces, capillaries, and into venous channels. The moving lymph and blood carry the neoplastic cells to distant parts. Therefore, metastasis to regional and distant lymph nodes and to other organs may occur while the growth is still relatively small at the site of its origin.

It would be of prognostic value if the cellular structure could be used to predict the course of the disease. This, however, is not entirely possible in carcinoma of the lung. The parent cell, the reserve cell, from which all carcinomas of the lung are derived, may remain undifferentiated or may differentiate into columnar cells or squamous cells, or all three types of cells may be mixed in the same growth. In men, over 50 per cent of the carcinomas of the lung are squamous cell, about 24 per cent reserve cell, 11 per cent columnar cell, and 12 per cent mixed cell carcinomas. In each histologic group there is a range of variations in cellular pattern, degree of differentiation, rapidity of growth, and the amount and kind of stroma induced. Regardless of the cell type, carcinoma of the lung may grow slowly or rapidly. The speed of growth is apparently governed by factors other than the cellular pattern.

The duration of the carcinoma and the survival time of the patient after the growth is detected may only be estimated because the telltale clinical signs and symptoms appear only after the carcinoma of the lung is well advanced. Survival time depends on the interplay of the behavior of the growth and the resistance of the host, local and constitutional. If curative measures are to be effective, obviously the growth must be recognized early since patients may present themselves with central nervous system involvement before attention is drawn to the primary site, the lung.

Recent studies compiled from the necropsy records of the Veterans Administration Hospital, Houston, Texas (A. M. A. Arch. of Path. 69:93, 1960) revealed that among 3,000 male patients examined, 363 had carcinoma of the lung. More than two-thirds of the patients with carcinoma of the lung were past 50 years of age. In 338 of the patients examined, the brain was included in the examination. Among these, intracranial involvement was recorded in 129 instances (38.1 per cent) of the brains examined. The presenting complaint of 30 of these patients had been clinical signs and symptoms of intracranial involvement. The frequency of intracranial involvement was exceeded only by metastases to lymph nodes (85.3 per cent), to the liver (44.3 per cent), and to the suprarenal glands (38.3 per cent). Carcinoma of the lung involved the brain more frequently in patients before the age of 50 years (54.6 per cent) and significantly less after 50 (33.4 per cent).

The time lapse between appearance of the symptoms of carcinoma of the lung and death of the 363 patients was one year or less in 309 (85 per cent). In the remaining patients, the duration of illness was unknown in 8 patients, was between 1 and 2 years in 32, between 2 and 5 years in 13, and was over 5 years in one patient.

As to the current methods of diagnosis, the following is revealing. Of the 363 patients who died with carcinoma of the lung, the clinical diagnosis was not made at all or not made with certainty in 70. The diagnosis was made by roentgenographic study alone in 42 patients. Exploratory thoracotomy confirmed the clinical diagnosis in 45 patients, pneumonectomy in 31, lobectomy in 12, and craniotomy in 7 patients. Of the remaining 156 patients, the diagnosis was established during life by bronchoscopic biopsy in 50, by bronchial

washing alone in 7 patients, by lymph node biopsy in 50, by skeletal biopsy in 14, by skin and muscle biopsy in 11, by needle biopsy of the liver in 8 and of the lung in 4, by thoracentesis fluid in 6, by laparotomy in 4, and by coughed-up sputum in 2 patients. According to these data, no microscopic diagnosis or surgical approach had been made in nearly one-third of the patients who died with carcinoma of the lung.

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Selecting the Operation for the Particular Patient in Cases of Duodenal Ulcer

Radical subtotal gastrectomy has proved its usefulness in the surgical control of the complications of duodenal ulcer, but at present the operation is being seriously challenged by procedures of less magnitude which appear to be equally or more therapeutically effective.

Bilateral subdiaphragmatic vagotomy combined with a conservative resection of the distal portion of the stomach has now been employed in several surgical centers for a decade, and careful follow-up data has revealed, thus far, that the rate of recurrent ulceration is astoundingly low. Also, the nutritional status of the postoperative patient has remained good, weight losses have been minimal, and hypochromic anemias have only rarely been encountered. In contrast, a significant percentage of patients subjected to a two-thirds or three-fourths resection of the stomach experience these complications.

The accumulated data of several clinical investigators who have expressed interest in vagotomy and antral resection reveal that, among a total of 3,052 patients who have undergone the combined operation, only 13 instances of recurrent ulceration have occurred at present. A sizable number of the entire group have been observed in excess of 5 years. The over-all clinical results have been satisfactory indeed, with but few exceptions. These facts become more impressive when one considers the critical evaluation employed and the careful follow-up studies performed in this relatively large series of patients by groups of clinicians who have devoted considerable time and effort toward the problems of ulcer disease (Table I).

There is one disadvantage, however, that one faces with the combined operation if it is selected for every patient who undergoes surgery for the control of the complications of duodenal ulcer. This is the operative mortality rate, which has ranged between 2 and 3 per cent in most reported series. The mortality is approximately the same as that associated with adequate subtotal resection, since both procedures entail division of the duodenum with its potential complications.

TABLE I. RESULTS OF VAGOTOMY AND ANTRECTOMY

	NUMBER OF CASES	LONGEST FOLLOW-UP (YEARS)	MORTALITY (PER CENT)	NUMBER OF RECURRENCES	
Edwards, Herrington et al.	800	13	3	5	2 patients, incomplete vagotomy 2 patients, functioning endocrine tumor
Fallis	500	10		4	
Martin	310	7.5		0	
Smithwick	305	10	2.3	1	1 patient, incomplete vagotomy
Crile	300	4		0	
Coffey	250	9		1	1 patient, incomplete vagotomy
Ransom	250	8		1*	*Suspected recurrence
Moloney (Oxford)	200	9		0	
Harkins	137	8	2.8	1	Possible stress ulcer
Total number	3,052			13 patients	

Since it now appears that with the use of the combined procedure the incidence of recurrent ulceration has been reduced to an extraordinarily low figure, it is important that greater emphasis be directed toward lowering the mortality rate of surgery for duodenal ulcer. This can best be accomplished by choosing the proper operation for the needs of the particular patient in question.

In the vast majority of operations for duodenal ulcer, the experienced gastric surgeon can carry out vagotomy and antral resection with a low morbidity and mortality rate. However, under certain exceptional circumstances, it may on occasion prove wiser to utilize a more conservative operative procedure, or what may be termed a compromise or alternate operation. A vagotomy with gastroenterostomy or pyloroplasty has proved its value in these situations. It should be emphasized that a mortality rate of 2 to 3 per cent following vagotomy and antral resection has largely been represented by series consisting of consecutive cases in which no particular consideration was given to the selection of an alternate procedure of less magnitude for certain poor-risk patients.

Vagotomy coupled with a drainage procedure is, perhaps, the operation of choice when confronted with the elderly poor-risk patient with coexisting renal, cardiac, or generalized vascular disease. Even in this type individual who presents with massive hemorrhage, the described operative procedure combined with transduodenal ligation and fixation of the bleeding vessel may prove lifesaving. The rate of recurrent ulceration following this conservative surgical approach is, no doubt, quite low in the patient in the advanced age group. Likewise, in the patient in the younger and middle age group who presents with a large, adherent inflammatory duodenal ulcer, it may, at times, prove better judgment to perform vagotomy and a drainage operation with the knowledge that a recurrent ulcer may follow. However, this wise selection at the time may mean the difference between life and death. Should a recurrent ulcer follow later, the combined procedure may then be utilized.

It should be stressed again that vagotomy and antral resection has proved to be an effective operative procedure for control of the complications of duodenal ulcer. If, after several additional years of follow-up study, the results are almost comparable to those being obtained at present, the combined procedure may well replace radical subtotal resection as the elective operation of choice. The mortality following surgery for duodenal ulcer is our major concern at present.

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Recent Advances in Surgery

CONDUCTED BY ALFRED BLALOCK, M.D.

RECENT ADVANCES IN CARDIOVASCULAR SURGERY

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THE epochal report of Blalock and Taussig[8] in 1945 on the creation of a shunt between the systemic and pulmonic circulations in the treatment of tetralogy of Fallot marks the beginning of an era unparalleled in surgical history. To be sure the stage was set by refinements in anesthesia, the growth of blood banks, the introduction of antibiotics, and the demonstration by Gross[29] that the patent ductus arteriosus could be treated surgically. Yet few, if any, who read this report could foresee that within the 15 years to follow virtually all the congenital and acquired lesions of the heart and great vessels would be successfully attacked. Looking back it is almost unbelievable that so much of genuine significance has been done. For instance, the heart-lung machines which were little more than laboratory curiosities for so long have been employed in thousands of cases. Arterial replacement has become commonplace with the reintroduction of homologous artery grafts and more recently the development of arterial prostheses made of synthetic materials. Finally, and to complete the circle, the lesions comprising Fallot's tetralogy are being corrected so that the Blalock-Taussig operation, after only 15 years, is of greater historical interest than therapeutic value.

From recent indications, however, the contemporary *cardiovascular period* is coming to a close. This does not imply a lack of interest in the field although there is a resurgence of interest in other fields. Rather, it is an indication that cardiovascular surgery is reaching maturity; that it has arrived at a point where, without the constant stimulus of one "first" after another, significant progress is still being made. With techniques standardized and with reliable equipment available, the surgeon is now able to turn his attention to the more basic problems of biochemical and physiologic alterations produced by disease on the one hand and by cardiovascular operations on the other.

This review is based upon papers concerned with cardiovascular surgical problems which were presented during 1959. Obviously, it is limited in scope and much of importance may have been omitted. On the other hand, an attempt has been made to include reports that are representative of the *New Look* in cardiovascular surgery.

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EXTRACORPOREAL CIRCULATION

A concern with problems related to extracorporeal circulation has been dominant during the past year. For the most part attention has been directed toward a better understanding and solution of problems arising from the use of pump-oxygenators, and toward extending the usefulness of this equipment. This interest is in contrast to previous years when there was great concern with the development of pump-oxygenators of newer design.

The complication of embolization during extracorporeal circulation was studied by Adams and colleagues[1] who had previously demonstrated the presence of fat emboli in tissues and urine following prolonged periods of cardiopulmonary bypass. In recent experiments, these workers added a nonionic wetting agent (Pluronic F68) to the blood used to prime the extracorporeal circuit and found that accumulation of fat emboli was largely prevented. This work may become even more significant when prolonged assistive perfusion is feasible.

Close and associates[16] carried out a somewhat similar study of the silicone (antifoam) content of tissues after extracorporeal circulation. Radioactive silicone was dissolved in ether, then applied to parts of a bubble oxygenator, and cardiopulmonary bypass was carried out. No significant silicone embolism of brain or of kidney was evident, thus demonstrating the efficacy of the method used of applying silicone. But the question of the actual hazard from the use of silicone remains unsolved.

The dangers of gas bubble (O_2) formation as a result of an induced temperature gradient or of a reduction in hydrostatic pressure at the site of arterial inflow has been alluded to in the past but little attempt has been made to demonstrate oxygen bubbles or to quantitate their formation. Donald and Fellows[25] in an extremely interesting study found that, when blood equilibrated with oxygen at 20° C. at one atmosphere pressure was subjected to an increase in temperature, the tension of the oxygen in the blood rose steadily. When a temperature differential of 17° C. was instituted, a steady release of gas bubbles was noted. There appeared to be a delay of about 10 minutes between institution of a temperature differential and the release of bubbles. When the temperature of an isolated volume of oxygen-equilibrated blood was raised rapidly from 20° to 37° C., no free gas bubbles were seen. This information may prove of value as the use of heat exchangers and the combination of hypothermia and extracorporeal circulation become more common.

One of the major problems in the use of the pump-oxygenator systems is that related to the use of whole blood. Burke and Gardner[12] studied the survival of red blood cells in dogs following total body perfusion and found that survival was reduced by 40 per cent over control values. Since similar results were noted when the system was primed with the dog's own blood, it was concluded that trauma resulting from pumping and oxygenating blood reduced the survival of red blood cells. Clinically this has not appeared to be a serious problem, however.

One of the most significant developments during the past year has been the introduction by Smith, Brown, and colleagues[69] of Edglugate magnesium as an anticoagulant preservative mixture for donor blood use in extracorporeal circulation. This mixture is composed of a chelating agent EDTA (ethylenediaminetetraacetic acid), sodium gluconate, magnesium chloride, and dextrose. It is prepared and sterilized in plastic bags and 500 c.c. of blood is drawn into each bag which is then stored at refrigerator temperatures. When ready for use, heparin and calcium chloride are added. Blood thus preserved has been used for priming a pump-oxygenator 1 to 5 days after procurement. It has been used in 115 open heart operations with no evidence of unfavorable effects. It was emphasized that this experience was limited to a combination of hypothermia and low flow perfusion techniques; however, there appears to be no reason why Edglugate blood would not be satisfactory for any type of perfusion.

For a time it was the custom, dictated largely by inadequate blood bank facilities, to draw blood for pump-oxygenator prime the day before operation. However, as demonstrated by Lobpreis,[46] there is a very real danger of inducing hypoglycemia by the use of "day-old" blood. He demonstrated that heparinized blood becomes markedly hypoglycemic, particularly when stored 12 to 24 hours and warmed just before use. Since in some systems the priming volume represents a significant part of the total blood volume, severe hypoglycemia may develop during extracorporeal circulation with severe sequelae. To prevent this complication it is recommended that 500 mg. of dextrose be added to each unit of heparinized blood immediately prior to use.

The study of metabolic alterations during extracorporeal circulation has continued with the result that there is now a clearer understanding of the total effects on the organism of cardiopulmonary bypass. The problem of metabolic acidosis was investigated by Magovern and associates.[48] By underoxygenating the blood a reduction in pH resulted which was then corrected either by adding sodium bicarbonate, by the creation of respiratory alkalosis, or by the addition of sodium lactate. Oxygen tension was determined from the pH, and the saturation of the blood at the corrected pH was compared to the calculated oxygen saturation of the blood at the same oxygen tension if the pH were not corrected. It was concluded that the Bohr effect raised the oxygen saturation of the blood about 15 per cent during its passage through the oxygenator. In addition it effected a greater A-V difference, implying increased utilization by the tissues. This suggests that the correction of metabolic acidosis during extracorporeal circulation results in improved oxygen uptake as well as improved dissociation of oxygen from hemoglobin.

Cardiac output and blood oxygen saturation were studied by Boyd and colleagues[10] in 34 patients following cardiopulmonary bypass. In those patients with a normal cardiac output and a mixed venous oxygen saturation of 60 per cent, no serious problems were encountered after operation. In contrast, of 15 patients with decreased cardiac output 10 failed to survive. The "sudden death" syndrome, observed by all engaged in this work, was invariably preceded by a period of low cardiac output. In a similar study, Kittle and coworkers[41] investigated right ventricular pressure in 22 patients with right

ventricular hypertension. These were continued for as long as 24 hours after operation. An increased right ventricular pressure after operation was followed by death or a severely complicated course whereas those without an increase in right ventricular pressure had an uneventful course.

Oxygen consumption during cardiopulmonary bypass was investigated by Starr[71] in experimental animals and in clinical cases. Oxygen consumption was noted to increase in a linear fashion with flow. Venous oxygen saturation also increased in like manner. He concluded that total body perfusion in humans at flows approximating basal cardiac output would not result in metabolic acidosis except under three circumstances: (1) low arterial saturation, (2) excessive skeletal muscle activity, and (3) prolonged perfusion.

Lindberg[45] reported a study of factors influencing the volume of venous return in animals during extracorporeal circulation. He suggested that intravascular pooling of blood in the presence of increased total peripheral resistance accounted for the decrease in venous return when extracorporeal circulation had been started. Studies of effects of temperature suggested that the rate of venous return paralleled the rise or fall of perfused blood temperature. Expansion of the circulating blood volume of the recipient animal was found effective in increasing venous return only if the perfusing blood temperature was high.

Blood changes during extracorporeal circulation of patients were analyzed by DeWall and associates[21] following experience with 350 perfusions. Plasma hemoglobin values were variable but in general were correlated with the length of perfusion time. Platelet counts tended to decrease after perfusion, but platelet depression, serious enough to account for bleeding, was not noted. Mild decrease in hemoglobin was observed during a 3-week postoperative period and mean pH values were within normal range at the end of the perfusion period.

Gibbon conceived the idea of a pump-oxygenator as a means of assisting the circulation in patients with pulmonary infarction more than 25 years ago and there appears to be a revival of interest in the use of the heart-lung machine for this purpose. Fisher and Smyth[27] carried out partial bypass for about 6 hours in a series of dogs with a delayed mortality of 85 per cent. Animals were responsive at the end of perfusion, only to die several hours later. It was observed that during perfusion serum inorganic phosphate levels increased, red blood cell destruction progressed, and venous return decreased, suggesting pooling of blood elsewhere in the venous system.

Kuhn and colleagues[43] studied the use of closed chest extracorporeal circulation without oxygenation in dogs in an attempt to determine the effectiveness of venoarterial shunting in maintenance of adequate proximal aortic pressure and, hence, coronary perfusion. In normal animals and in those with decreased blood pressure following coronary embolization, an increase in proximal aortic pressure could not be achieved. It was necessary to increase resistance by obstruction of the lower abdominal aorta in order to increase proximal aortic pressure. It would seem that the same thing can be accomplished with pressor amines and in fact it is a part of accepted therapy for severe coronary thrombosis.

Veith and Thrower[76] reached similar conclusions regarding assisted circulation in heart failure, using sodium excretion in response to a saline load in animals with pulmonary stenosis and tricuspid insufficiency. It was found that cardiopulmonary bypass was not effective in increasing sodium excretion in contrast to its effect in normal animals.

The effect of prolonged venoarterial pumping on the circulation of animals was reported by Hamer and associates.[32] The method involved withdrawal of blood from the superior vena cava and pumping the blood into the terminal aorta without oxygenation. At flow rates below 30 c.c. per kilogram per minute, oxygen saturation of the shunted blood remained constant. However, at flow rates greater than 30 c.c. per kilogram per minute, there was a progressive fall in the oxygen saturation of the shunted blood. The longest period of venoarterial pumping was 25 hours, and no major changes in blood constituents, renal function, or acid-base balance were observed.

HYPOTHERMIA

One of the most important reports of the year was that of Sealy and associates[64] on hypothermia and extracorporeal circulation for open heart surgery. These workers introduced a heat exchanger for blood cooling and rewarming that, because of the rapidity with which the body temperature may be increased or decreased, overcomes many of the objectional features of hypothermia. For uncomplicated defects, temperatures of 28° to 32° C. were employed with low flow rates. In conditions requiring a longer period of perfusion, temperatures of 26° to 30° C. were utilized. In the management of extremely complicated defects, temperatures of 9° to 20° C. were employed with hypothermic cardioplegia. In some of these patients all circulation was stopped for periods of 7 to 10 minutes, thus finally realizing suspended animation in the human.

Peirce and Dabbs,[57] also pioneers in the combination of hypothermia and extracorporeal circulation, have studied metabolic acidosis and oxygen consumption during and after total cardiopulmonary bypass with and without hypothermia. The development of metabolic acidosis and oxygen consumption are inversely related. Anesthesia and inorganic acids in banked blood contribute to metabolic acidosis. Decreased oxygen consumption and increased A-V difference correlate with the development of metabolic acidosis. Hypothermia, leading as it does to a decreased oxygen consumption, permits a decrease in perfusion rate without the fear of metabolic acidosis.

Moghul and associates[53] studied the pressure tolerance of rats at normal temperatures and under hypothermia. Animals supercooled to suspended animation tolerated rapid decompression from pressures of 500 pounds per square inch maintained for 5 minutes. Above 650 pounds of pressure traumatic air embolism occurred.

The sensitivity to radiation following hypothermia was studied by Benvenuto and Lewis.[5] It was found that deep hypothermia protected rats against a single x-ray dose of 800 r and of 1,500 r respectively, as compared to controls. This study suggests interesting possibilities in the therapy of cancer.

About 2 years ago, Wax and Webb showed that the cooled dog's heart could be transplanted after several hours with resumption of function. Barsamian and his group[4] have gone one step further and by combining mechanical dehydration with supercooling, that is, to –8° C., demonstrated that hearts could be transplanted with restoration of their normal beat.

A study of the effect of administration of heparin, glucose, and heparin-glucose was investigated by Caranna and associates[14] as a means of lowering the mean terminal temperature of the hypothermic dog. In a control group, ventricular fibrillation or cardiac arrest occurred at the mean temperature of 19.4° C., whereas in the group treated with heparin, the mean temperature was 14.7° C.

Enerson and co-workers[26] introduced the term "selective cooling index" as the relationship between the actual and the theoretical heat exchange. It is derived from the flow rate, from the line temperature gradient, and from the temperature change and weight of the animal. It is thought that this "selective cooling index" may provide a uniform standard for evaluation of the efficiency of heat exchangers and of internal hypothermia.

Johnson and co-workers[37] experimented with the prevention of ventricular fibrillation during profound hypothermia using quinidine. Immediately prior to hypothermia, intravenous quinidine was administered and the effect was to prevent ventricular fibrillation. The mechanism for development of ventricular fibrillation during profound hypothermia is that of unequal cooling and rewarming of the heart which results in areas of unequal excitability and conductivity. Thus, response of the cardiac muscle to a stimulus is not uniform and the stage is set for the development of abnormal impulses and irregular conduction. Quinidine, by suppressing the excitability and electrical conductivity of the cardiac muscle, probably promotes the development of uniform cardiac response as the muscle is rewarmed.

MYOCARDIAL METABOLISM, CONDUCTION, AND CARDIOPLEGIA

Dissatisfaction with potassium-induced cardioplegia by the Melrose technique has led to the investigation of other more efficient methods of arresting cardiac action. Dodrill and Takagi[24] combined ATP (adenosinetriphosphate) with potassium citrate to produce cardioplegia in dogs. Resuscitation was accomplished with ease after one hour of arrest. They concluded that the anaerobic material ATP maintains metabolism of the myocardium during arrest. Gott and associates[28] biopsied human hearts during potassium citrate arrest and selective hypothermic arrest and analyzed the specimens for energy substances. Following potassium citrate arrest, it was found that ATP, phosphocreatine, and glycogen levels were more rapidly reduced than was observed in selective hypothermic arrest. It was also noted that the tissue lactic acid rose more rapidly with potassium citrate-induced arrest. It appeared that, for cardioplegia, selective hypothermic arrest was superior to potassium arrest in maintaining the myocardial energy resources.

Myocardial metabolism during elective cardiac arrest was studied also by Hall and associates[31] who made serial biopsies of the myocardium during potassium-induced arrest. The results of their experiments indicated that hypothermia prevents the excessive loss of myocardial glycogen and possibly of phosphocreatine, and may prevent the continued loss of glycogen following the period of arrest. When ATP is added to the arresting solution, it may provide a source of intracellular ATP but this may rapidly be utilized during the arrest period by conversion into phosphocreatine which is then reconverted to ATP and utilized after the arrest period. The use of hypertonic glucose, possibly with insulin, may have merit in providing the myocardium with a readily available source of glycogen.

A magnesium-charged cationic resin was employed by Clark[15] to remove calcium from flowing arterial blood in the perfusion of isolated hearts. By equilibrating the resin with solutions containing sodium, potassium, and magnesium, it was possible to maintain normal levels of these ions. Continuous perfusion of the heart with low calcium blood resulted in sustained arrest and at the same time assured a well-oxygenated pH-controlled myocardium. Isolated hearts, perfused in this manner, had an oxygen consumption of about 25 per cent of that of an empty beating heart. This method may prove to be a solution to the problem of elective cardiac arrest at normal temperatures.

Topical cooling of the heart by placing cold saline into a cradle formed by the pericardium was described by Shumway and Lower[67] and is a simple and apparently effective method of inducing selective myocardial hypothermia during anoxic arrest.

Headrick and co-workers[34] developed a method for safely prolonging induced cardioplegia which consisted of cannulating the coronary arteries through an incision in the descending aorta after occluding this vessel proximal to the brachiocephalic trunk. The myocardium is then perfused with oxygenated blood containing about 15 mEq. of potassium per liter. In 4 animals, cardiac resuscitation was accomplished after 3 hours of cardioplegia. Urschel and Greenberg[75] induced differential cardiac hypothermia by perfusing the myocardium through the aorta with whole oxygenated blood, blood mixed with saline or dextran, and finally with Ringer's lactate solution. Because of the low viscosity at hyperthermic temperatures, and its electrolyte composition, Ringer's lactate was found to be most desirable.

Willman and colleagues[79] found that 30 minutes of cardiac arrest induced by acetylcholine, potassium citrate, or anoxia severely impaired the ability of the canine heart to work, whereas arrest of 20 minutes was less harmful, although there was a significant depression of the myocardium. Digitalis glucosides were given just before cardioplegia, and when the heart was cooled there was an increased work capacity as compared with the normothermic or nondigitalized heart.

Weirich and associates[77] observed that following cardiac arrest induced with acetylcholine, ventricular function curves were similar to those obtained prior to cardiopulmonary bypass, and this was true when the period of arrest was

from one second to 10 minutes; however, when the arrest lasted from 15 to 20 minutes, there was deterioration in ventricular function. The severest alteration in ventricular function followed potassium citrate-induced arrest.

Many studies on myocardial function and conductivity have been made. Bloodwell and co-workers[9] used a strain gauge arch and found that the contractile force of the heart could be measured in 42 patients undergoing operations with cardiopulmonary bypass. For the first time it was possible to study the direct effects of digitalis, sympathomimetic amines, and anoxic arrest on myocardial contractility in man. It was demonstrated that epinephrine and norepinephrine produce almost identical increments in myocardial contractility. This countered previous assumptions that norepinephrine has little effect upon cardiac output. A profound increase in contractile force following administration of digitalis preparations clearly demonstrated the increase in myocardial contractility produced by these drugs in the nonfailing human heart. This finding should give the surgeon some support in attempts to encourage the cardiologist to digitalize the patient *before* rather than *after* heart failure is evident clinically.

Thrower and co-workers[74] studied the relationship between symphathoadrenal function, acid-base derangements, and ventricular contractile force. They used a strain gauge arch following infusion of catechol amines and correlated results with the pH and CO_2 combining power. Infusion rates of levarterenol or epinephrine had to be continually increased after the first 30 to 35 minutes if the ventricular contractile force was maintained at 100 per cent above control. After about 90 minutes, the contractile force failed to increase with increased infusion rates. Generally, there was a decrease in the contractile force responsiveness prior to decrease in blood pressure responsiveness and this loss paralleled a decrease in plasma CO_2 combining power. No difference was evident in response obtained with epinephrine as compared with that of levarterenol. When sodium lactate was infused, there was an increase in arterial pH but no effect on the CO_2 combining power of plasma and the cardiovascular response was unaffected. When sodium bicarbonate was given, it not only corrected the arterial pH but increased the CO_2 combining power and increased the responsiveness of the cardiovascular system to injections of levarterenol. When an organic carbon dioxide buffer (THAM) was infused, there was an increase in pH, CO_2 combining power, ventricular contractile force, heart rate, and pulse pressure. After an animal had become refractory to infusions of levarterenol, it was observed that single injections of other pressor amines had a decidedly better effect on contractile force and blood pressure. When the animals became refractory to these substitutes, it was found that levarterenol infusions again produced responsiveness.

In an ingenious experiment by Sabiston and associates[62] the coronary circulation of an isolated heart of a dog was perfused with oxygen in the gaseous state. It was observed that the beat of the isolated heart could be maintained for periods up to 8 hours. Perfusion of the heart in situ with gaseous oxygen was performed with later reversion to blood and the re-establishment of normal

circulation. These studies indicate that oxygen perfused in the gaseous state is utilized by the heart and that cardiac contraction may be maintained for prolonged periods when it is perfused with oxygen alone.

The problem of injury to the conduction system during intracardiac operations remains unsolved. Allen and associates[2] have used a supravital stain to identify the bundle of His. They applied a 4 per cent elemental iodine in 10 per cent sodium iodide in order to delineate the cardiac conduction system. The method was applied in 8 animals with satisfactory visualization of the bundle of His in 7 of the group. Of three clinical cases in which this staining technique was used, two showed satisfactory visualization while in the third case the conduction system was not delineated and this patient developed complete heart block following repair of the defect. There is some recent evidence, however, that 10 per cent iodide is damaging to the conduction system. A surface electrode was used by Stuckey and associates[72] to identify the bundle of His during cardiotomy. This method proved highly effective in locating the conduction system in the experimental animal and has been successfully applied in human beings.

Kittle and Crockett[41] found that, among 254 patients with mitral valvotomy, atrial fibrillation occurred after operation in 41 of 155 patients who had a normal rhythm prior to operation. It was concluded that the combined use of digitalis and quinidine postoperatively was beneficial in preventing arrhythmia. Conversion of postoperative atrial fibrillation to sinus rhythm usually may be accomplished, whereas conversion of atrial fibrillation existing prior to operation is more difficult.

CIRCULATION OF THE HEART

Talbert and Sabiston[73] reported the results of a quantitative study concerning the effect of radiopaque contrast media on coronary blood flow. Pressures and flow in the coronary system of dogs were measured at constant intraaortic pressures. Normal saline solution, Renografin, and 70 per cent Urokon, were used. When perfused into the myocardial vascular bed, the compounds produced consistent changes which were directly proportional to the quantity of media injected. The response was characterized by an immediate and brief reduction in coronary flow, followed by an increase in flow with ultimate return to the control level. Changes noted were transient with return of coronary flow to normal within 1 to 4 minutes. The authors concluded that such changes do not appear to constitute a contraindication to the use of radiopaque media in clinical coronary arteriography, and are similar to those observed in blood vessels exposed to contrast agents in other part of the body. This work seems significant in view of the increasing interest in the direct surgical attack on coronary arterial disease.

A square-wave electromagnetic flowmeter was applied to intact blood vessels for measurement of coronary blood flow by Marston and associates.[49] The significant findings from the use of this instrument in anesthetized open chest

dogs were as follows: A measurable reactive hyperemia occurs routinely following momentary occlusion of the coronary artery. Both auricular and ventricular premature contractions resulted in a decrease of coronary blood flow of approximately 50 per cent and were differentiated by their various effects upon the flow recorded. Administration of a mixture of 50 per cent cyclopropane and 50 per cent oxygen produced a decrease in blood flow of about 40 per cent. Following the administration of norepinephrine, the coronary flow increased 300 per cent. A similar, but less pronounced, effect on flow was noticed following the injection of Vasoxyl. The administration of a mixture of 50 per cent carbon dioxide and 50 per cent oxygen produced a 50 per cent increase in coronary blood flow, slight bradycardia, and a fall in blood pressure. The "kinks" seem to have been worked out of the square-wave electromagnetic flowmeter and it should become a valuable tool for blood flow measurement.

Senderoff and co-workers[65] investigated the effect of cardiac irradiation upon myocardial vascularity. Ligation of an anterior descending branch of a left coronary artery was done in dogs 4 to 6 days and 6 months, respectively, following irradiation of the heart. The dogs were then studied for survival, for pressure in the artery distal to the ligature, and for backflow from the distal severed end of the artery. Survival in a control group (nonirradiated) was 11 per cent, whereas in the two irradiated groups 40 and 75 per cent, respectively, survived. Similarly there was an elevated pressure distal to the ligature in the two irradiated groups and an increased backflow of blood, being greatest in the group tested at 6 months. It appears, however, that longer periods of observation are necessary in order to determine whether there will be any deleterious effects of irradiation on the heart.

Knock[42] compared radical cardio-omentopexy with the Beck I and with the Vineberg sponge operations for revascularization of the heart. His method consisted of loosening the epicardium with a 5 per cent solution of sodium salicylate in 25 per cent glucose, and then removing it surgically from the outer surfaces of both the right and left ventricles. Multiple vascular strips of omentum were then implanted on the left ventricle and a wide strip of omentum was laid over the origin of the branches of the left coronary artery, over the conus arteriosus, and onto the origins of branches of the right coronary artery. The left circumflex and left anterior descending coronary arteries were both constricted by Ameroid constrictors as a challenge. Of the control dogs operated on, all died. Six dogs treated by the Vineberg procedure died. Of the 10 animals treated by the Beck I method, 3 survived and were capable of strenuous exercise. Of the dogs treated by radical cardio-omentopexy, 7 survived and were capable of exercise.

Cannon and Longmire[13] have considered the rationale and technique of coronary endarterectomy for angina pectoris. Their experience is based upon animal experimentation, upon pathologic study of coronary atherosclerosis and upon 9 cases of severe angina pectoris treated by endarterectomy. These workers are strongly convinced of the surgical feasibility of disobstructing the coronary arteries as they are involved in severe angina pectoris. Proof has

been produced of the continued patency of the coronary circulation after operation in the animal but definite proof of such continued patency of the coronary arteries in the human has not yet been established.

DIAGNOSTIC TECHNIQUES IN CARDIOVASCULAR DISORDERS

The use of indocyanine dye for indicator dilution techniques was described by Hyman and associates.[36] The method employed consisted of placing a cardiac catheter into the distal right or left pulmonary artery and another catheter in the main pulmonary artery. Green dye was then injected into the distal catheter and sampling done from the proximal one. Simultaneous sampling was done from a femoral artery through a Colson densitometer. If a shunt was evident the withdrawal catheter was moved to the right ventricle and then to the right atrium and finally to the superior vena cava. Dye dilutions were repeated in each chamber. This method was used in 44 patients and proved to be more accurate than the oxygen method for the detection and quantitations of left-to-right shunts. A similar technique using a single catheter has been described by Pfaff and his group.[58] This method, while simpler than that just mentioned, does not permit quantitation of shunts.

Detection and quantitation of pulmonic or tricuspid regurgitation may be accomplished with indocyanine dye, according to Collins and co-workers.[17] A double lumen catheter is placed with openings on each side of the valve to be studied. Dye is injected distally and sampling is carried out proximally. This method proved highly satisfactory in measuring valvular insufficiency.

The degree of mitral insufficiency was measured in the dog by DeWeese and associates[23] using RISA. Alteration in indicator curves correlated well with anatomic degrees of mitral insufficiency. Similarly Jontz and colleagues[38] found that regurgitation could be quantitatively studied by left ventricular cinecardioangiography and this method proved to be more accurate than pressure curves in assessment of mitral regurgitation. It should be pointed out, however, that these animals had acute mitral insufficiency. The situation with chronic mitral insufficiency is somewhat different and estimation of the degree of mitral insufficiency may be difficult with angiographic techniques.

A technique of intravenous aortography was described by Bernstein and associates[7] in which a preliminary arm-to-abdominal aorta circulation time is determined by the use of radioactive Renografin with a scintillation detector placed over the abdominal aorta. Following the injection of dye into an arm vein and after a pause equal to the arm-to-abdominal aorta circulation time, roentgenograms are made at the rate of one per second in two planes, for 5 to 10 seconds. Films of excellent quality were thus obtained without the risk of direct aortography.

Williams and colleagues[78] described a method for selective roentgenographic demonstration of the coronary arteries and other visceral branches of the aorta. The Seldinger technique was used to introduce a specially designed catheter by way of the common femoral artery. With the tip of the catheter in the

peripheral portion of the aortic stream and at the level of branches to be visualized, the contrast material was injected by hand. Infarction resulted from the technique in one instance.

Damage from aortography may be a result of repeated injections. Killen and colleagues[39] demonstrated significant neurologic changes in the dog with repeated injections of the commonly employed contrast agents. In a similar study, Read[59] observed that red cell agglutination may occur with agents that have a high osmolality and that this interference with the stability of the red cell stream may be the basis for the pathologic effects noted.

CORRECTIVE SURGICAL TECHNIQUES

Problems in the management of coarctation of the aorta were reviewed by Groves and Effler.[30] The authors stress their belief that an aggressive attitude should be adopted in the treatment of the infant in congestive heart failure associated with coarctation, although the majority of these patients have other cardiac anomalies. Aortic hypoplasia may also exist in the proximal portion of the coarctation but apparently is well tolerated after coarctectomy. Surgical risk in the older patient is high, although many in the fifth decade may be treated with success. The postcoarctation abdominal pain syndrome is thought to be associated with complete correction of the coarctation and with maximal increase in visceral circulation. The finding of a rather diffuse panarteritis suggests some induced vascular damage following coarctectomy. The use of grafts should be avoided when possible unless an anastomotic lumen of 1 cm. may be effected. Following operation, a number of these patients tend to have a labile blood pressure which renders it difficult to determine those who are truly hypertensive. It is suggested that hypertension in these patients is due to an inelastic central arterial reservoir rather than to residual obstruction at the anastomotic site. Therefore, it may be possible that some of the factors responsible for hypertension in the untreated patient may be present.

Experience with the early correction of coarctation of the aorta and patent ductus arteriosus was reviewed by Burford and associates.[11] All of the patients studied were in cardiac failure and had marked cardiac enlargement. Diagnosis was established by the flush technique which showed a significant pressure gradient. At the time of operation, the 16 patients in the series were, on the average, about 6 weeks of age. The operative mortality was 44 per cent. Considerable anatomic variation in the relationship of the coarctation with patent ductus arteriosus was observed. Animal experiments, conducted to determine the effect of patent ductus arteriosus both above and below the coarctation, proved that these lesions together constitute a lethal combination. This observation confirmed the clinical findings.

A group of 20 patients with obstructive lesions of the lower thoracic and abdominal aorta were studied by Morris and co-workers.[55] On the basis of clinical and morphologic characteristics, these subisthmic lesions were divided into three levels of involvement, namely: lower descending thoracic aorta, upper abdominal aorta, and lower abdominal aorta above the bifurcation.

There were four cases with subisthmic coarctation of the lower thoracic aorta. The most prominent feature was the minimal development of collateral circulation in patients who had other manifestations of coarctation. There were four instances of an obstruent process involving the abdominal aorta. In this group, hypertension was more severe. The third group included individuals with lesions of the lower abdominal aorta proximal to the bifurcation. These lesions were considered to be the result of intimal thickening in the case of 5 young adults. In 12 other cases with ages in the fourth and fifth decades, thromboobliterative changes had resulted from arteriosclerosis. Subisthmic coarctation of the lower thoracic aorta was treated by resection and graft replacement. Obstruction of the upper abdominal aorta was treated by the bypass principle and lesions in the lower abdominal aorta were treated by endarterectomy.

Long and co-workers[47] described the subtotal and total replacement of the aortic valve with a plastic aortic valve prosthesis. This valve was constructed from Silastic, one of the rubbery silicone group. Because of their chemical inertness, lack of toxicity, and favorable flexion life, these materials seem most suitable for this purpose. The two types of prostheses are a flap valve for partial or complete restoration of aortic valve function and a bicuspid valve with self-contained annulus for total replacement of the aortic valve. The flap valve was successfully inserted in the subcoronary position in 5 dogs which survived from 5 to 29 days and was used successfully in one patient with severe aortic stenosis who remained well for one year. A second patient, similarly treated, was well and active for 2 months only to die from accidental causes. The bicuspid prosthesis for total replacement of the aortic valve was inserted in dogs but without long-term survival. Remaining to be solved are the problems of fibrin formation about the valve and damage to the conduction mechanism.

Surgical experiences in the treatment of 5 cases of congenital mitral stenosis and 2 cases of mitral insufficiency were related by Starkey and associates.[70] All of the children were underdeveloped and in congestive failure with severe respiratory infections and dyspnea. Three of the 5 patients had had repeated bouts of syncope with cyanosis. Physical examination revealed cardiac findings compatible with mitral stenosis and catheterization data were confirmatory. Four patients were operated upon by the "closed" method and one by the "open" method using a pump-oxygenator. In 3 patients, the valves were flat, thickened, and diaphragmatic with poorly defined commissures which were incised with a knife. The fourth case showed a well-defined funnel and commissures. The fifth patient had a funnel valve but practically no commissural definition. There were two deaths in the series.

A group of 180 patients with atrial septal defects complicated by pulmonary hypertension were treated surgically by Liddle and Jones.[44] Fifteen of the patients had pulmonary artery pressures in excess of 50 mm. Hg. Five of these succumbed at operation and two were not benefited by closure of the defect. A review of these 15 patients suggests the following four clinical and laboratory observations to be related to surgical failure: (1) presence of

cyanosis, (2) history of congestive heart failure, (3) severe right ventricular hypertrophy, and (4) marked discrepancy in vessel size by chest roentgenograms. When two or more of these observations are made in a patient, the authors concluded that there probably exist irreversible pulmonary vascular changes.

In a similar study, McGoon and co-workers[52] reviewed their experience in 119 cases of atrial septal defect and analyzed factors affecting surgical mortality rate. These factors are as follows: (1) history of congestive heart failure, (2) markedly elevated right atrial pressure, (3) large right-to-left shunt, (4) severely elevated pulmonary artery pressure, and (5) markedly increased pulmonary vascular resistance. If none or only one of the afore-mentioned factors was present the mortality rate was less than 5 per cent, and in patients in whom two or more of these factors existed, the mortality rate was 50 per cent.

A group of 54 cases of endocardial cushion defects was reviewed by McGoon and associates[51] and classified into partial common atrioventricular canal, complete common atrioventricular canal, ventricular septal defect with cleft atrioventricular valves, and common atrium. The importance of the frontal plane configuration in the vectocardiogram to diagnosis of this condition is emphasized. Surgical repair with the aid of extracorporeal circulation consists in closing clefts in atrioventricular valves and closing the ostium primum defect with a prosthesis. If a ventricular septal defect is present it is closed with a separate prosthesis through the right ventricle. Of 32 patients with partial atrioventricular canal there were two operative deaths and one late death. Twenty of the 29 patients are believed to have had complete repair. Of 15 patients with common atrioventricular canal, 11 died after operation, and two others died at home of other causes. Emphasized is the importance of restoring function of the atrioventricular valves and of avoiding injury to the conduction mechanism.

Morrow and Braunwald[56] reported a series of 3 patients in whom left heart catheterization studies had evidenced significant gradients across the aortic outflow area, but at operation no discrete site of obstruction was found in 2 patients while in the third case there was an area of subvalvular stenosis. The authors emphasize the clinical and hemodynamic features which may aid in distinguishing functional stenosis from the more usual forms of aortic stenosis. These features include a thrill and murmur more prominent at the apex than in the aortic area, the lack of poststenotic dilatation of the aorta, and the evidence of left heart catheterization of subvalvular rather than valvular obstruction.

Senning[66] of Stockholm reported the successful complete correction of transposition of the great vessels by internally transposing caval and pulmonary venous return. This is the first recorded instance of such a procedure having been successfully performed.

ATHEROSCLEROSIS AND OCCLUSIVE VASCULAR DISORDERS

Following the report of Shaw regarding occlusive disease of the superior mesenteric artery, Derrick and co-workers[20] studied 110 unselected aortas at

necropsy. There was atherosclerotic narrowing of the celiac artery in 44 per cent and of the superior mesenteric artery in 37 per cent indicating the frequency with which these important vessels are involved.

In a very interesting and timely study, Morris and associates[54] reviewed the arteriograms of 246 patients and categorized the anatomic and pathologic variations in the popliteal arteries. In about 90 per cent of cases, the anterior tibial artery arose as a major branch rather than a division of the popliteal artery and its origin was about 5.8 cm. below the knee joint. The posterior tibial artery arose as a branch of the popliteal about 5.8 cm. below the joint space. The peroneal arose from the posterior tibial artery. The distal popliteal usually had but one small branch which may account for the fact that it was consistently less involved in arteriosclerosis than the more proximal portion of the artery.

McAllister and associates[50] studied the effects of experimental atherosclerosis in the canine and found that dogs which were exercised had more serious atherosclerosis than those which were sedentary. Then, they concluded "that individuals with known atherosclerosis and abnormally high serum cholesterol would be ill-advised to indulge in vigorous or protracted exercise." Further, "it is not possible for one to chronically overindulge in a high fat, cholesterol diet and expect to work it off with weekend exercises."

One of the most significant reports of the year was that of Crawford, DeBakey, and their collaborators[18] concerned with evaluation of late failures following corrective operations for atherosclerosis. A total of 1,225 patients with aortoiliac or femoropopliteal occlusion were followed from 1 to 6 years. At the time of discharge from the hospital 96 per cent of patients with aortoiliac and 88 per cent with femoropopliteal occlusion had successful results. In contrast, follow-up revealed a failure of 6.2 per cent of the group with large vessel obstruction and in 21 per cent of the group with femoropopliteal occlusion. Development of false aneurysms, erosion of a graft into the duodenum, recurrent obstruction due to kinking of the graft, unrecognized proximal and distal disease, and progression of pre-existing disease all were causes for failures.

A study of hyperemia of the limb following reconstructive arterial surgery in extremities with obliterative arterial disease of long standing was made by Simeone and Husni.[68] Twenty-nine patients with occlusive arterial disease of the lower extremity (32 extremities) were studied before and after re-establishing arterial continuity by reconstructive surgery. Fifteen patients (16 extremities) showed obvious postoperative hyperemia, both clinically and by measurement in the laboratory. Upon exposure for 90 minutes to an environment which normally induced maximal reflex vasoconstriction, hyperemia persisted while the normal extremity promptly cooled to room temperature. The hyperemia lasted from one to 6 weeks. The phenomenon was least pronounced when the obstruction involved a short segment of artery and the bridging collaterals were large. It did not occur when reconstruction was performed for acute traumatic lesions or when the arterial operation proved unsuccessful. The investigators concluded that this phenomenon is a result of loss of tone by arteries subjected to a reduced tension for long periods of time.

Rendleman and associates[60] studied factors affecting the deposition of atheromas in the aorta and vascular grafts in rabbits. Segments of the aorta were occluded and hypassed with Dacron-Teflon prostheses. The animals were then sacrificed. There were atherosclerotic changes in the grafts and in the aorta, but no changes were noted in the bypassed aortic segments with intact vasa vasora but no luminal flow. This study suggests that luminal blood flow is necessary for atheroma formation.

VASCULAR PROSTHESES

There has been much less concern this year with the development of new vascular prostheses. Hardy and colleagues[33] constructed straight tubes from a polyacrylic ester rubber in foam form. The tube was devised so that the foam material was bonded to a two-way stretch Dacron fiber. These prostheses were then implanted into the abdominal aorta and the femoral arteries of dogs. Early results of this prosthesis were encouraging.

Experimental use of Teflon prostheses for elongation of the inferior vena cava in the Baffes operation was reported by Davalos and associates.[19] Tubes varying in length from 3 to 7 cm. were sutured end-to-side to the inferior vena cava and end-to-side to the right atrium in normal dogs. These tubes were of knitted Teflon, 13 mm. in diameter, and the porosity was reduced by impregnation with a Teflon suspension. All of the grafts remained patent up to 6 months when the study was terminated.

VENOUS THROMBOSIS

Berg and co-workers[6] reported the use of radioactive sodium and RISA in the evaluation of the edematous leg. The half-time of the rate of disappearance of subcutaneously injected Na_{24} was taken as an index of venous outflow from the lower extremity, and the half-time of the disappearance of subcutaneously injected RISA was indicative of the status of lymphatic outflow of the extremity. Ten subjects with normal legs and 18 subjects with abnormal legs were examined. Cases of cellulitis showed increased venous absorption and decreased lymphatic absorption. Arterial insufficiency delayed absorption of both systems. The existence of major venous obstruction did not cause delay of venous drainage as measured by this method. Cases of postphlebitic edema showed delayed absorption of Na_{24} while others had normal disappearance of Na_{24} with delayed absorption of RISA. Several cases of acute thrombophlebitis demonstrated a compensatory increase in lymphatic flow in the presence of edema due to acute venous obstruction.

DeWeese and associates[22] evaluated thrombectomy in the management of iliofemoral venous thrombosis, and their findings are of interest and importance. Thrombectomy without distal vein ligation was performed on 18 extremities of which 8 were considered complete procedures. Cases operated upon showed less early morbidity, particularly with regard to swelling, vasospasm, and gangrene. The morbidity of chronic swelling remained a problem. The evaluation indicates that return of resting venous pressure to normal, and

persistent patency of veins after thrombectomy may be attained by this procedure. When there is evidence of vasospasm or of imminent gangrene, thrombectomy is of special value.

MISCELLANEOUS

Measurement of collateral circulation induced by enteronephropexy was made by Riley and Cantrell.[61] In a control group, average renal artery backflow was 0.5 c.c. per minute. In the first experimental group, in which enteronephropexy alone was performed, the average renal artery backflow was 1.1 c.c. per minute. In the second experimental group where phenol was applied to the raw surface of the kidney and combined with enteronephropexy, the average renal artery backflow was 2.2 c.c. per minute. In the third group in which acute renal ischemia was present, phenol application and enteronephropexy were performed and the average renal artery backflow was 11.6 c.c. per minute. They concluded that significant renal collateral circulation may be induced by enteronephropexy with the volume of flow strikingly increased in the collaterals. It was thought that the collateral channels communicate with glomerular vessels and may assume to some degree the role normally played by the renal artery of supplying blood to the glomerular vascular bed.

The pulmonary diffusing capacity in congenital and in rheumatic heart disease was studied by Auchincloss and associates.[3] Sixteen patients with intracardiac defects, 13 with rheumatic valvular disease, and 19 normal subjects were observed. In 10 patients with intracardiac septal defects, there were significantly elevated values. In 9 of this group, there was an increase of pulmonary blood flow. In patients whose septal defects were accompanied by pulmonary hypertension, normal or insignificantly elevated values were noted. The conclusion reached was that pulmonary blood flow and diffusing capacity are related quantities, and that the pulmonary vascular complications in patients with septal defects may be associated with impaired diffusion. In a somewhat similar study, Schramel and associates[63] measured pulmonary diffusion (D_{co}) before and serially after cardiopulmonary bypass. In almost every case there was a significant reduction in D_{co} immediately after operation and this defect persisted for as long as 6 to 8 weeks.

Hillman and colleagues[35] studied femoral arteriovenous fistulas in the dog with serial arteriography and concluded that arterial collateral development is less intense than formerly thought to be. In addition, there was evidence to support the contention that increase in bone length in the presence of an arteriovenous fistula is a result of venous stasis and not of arterial collaterals. This observation is extremely interesting since it contradicts accepted theories regarding collateral circulation in arteriovenous fistulas.

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Surgical History

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THE ROLE OF THE MILES ABDOMINOPERINEAL EXCISION IN THE HISTORY OF CURATIVE RECTAL CANCER SURGERY

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THE history of surgery performed for malignant lesions of the rectum indicates that factors responsible for failures of operative cure have changed markedly during the past 150 years. The almost uniformly unfavorable operative results observed a century ago often have been erroneously ascribed to the leaving behind of muscular, vascular, and lymphatic pathways of tumor dissemination with the inadequate excisions employed; it seems quite evident, however, that at most only a few patients were sacrificed by these limited procedures. The majority of curative failures of that era, doubtless, were a direct result of the high operative mortality; the chief reason for surgical failure, thus, was failure of the patients to survive the operations. Volkmann expressed in his clear and precise manner the popular feeling of that day in regard to treatment of patients with rectal cancer: "Referral to the surgeon is referral to the grave."[4]

Later, with the introduction of anesthesia, asepsis, and antisepsis, operative mortality fell and results improved. By the last quarter of the nineteenth century, wide excision ("extirpation") was being done by many European surgeons; some of the patients who had lesions which had spread beyond the rectal wall were presumably offered an opportunity for cure. And by 1900, with the Volkmann-Kocher-Kraske technique of removal of all grossly visible tumor, results had so improved that 15 to 20 per cent of patients operated upon survived three or more years postoperatively.

Further betterment of results of surgery was made possible about the turn of the century by the introduction of the combined approach, abdominal sacral or abdominal perineal. In addition to the acknowledged superiority in adequacy of operative scope, other less evident features of the combined approach favored statistical betterment. For example, patients with liver metastases, with abdominal carcinomatosis, and those with unresectable tumor spread could be listed as "palliative" and no longer tallied as curative failures.

During the past half-century, the abdominoperineal excision, based on the 50-year-old operation of Miles, has become the standard procedure in treatment

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of cancer of the rectum. Today, even those who do not employ the Miles technique use its survival accomplishments as the standard of comparison. The history of rectal cancer therapy and the Miles operation allows some insight into the problems currently faced in the surgical treatment of rectal cancer.

The first successful surgical excision of a rectal cancer is credited to J. Lisfranc,[9] on Feb. 13, 1826. In 1833 he reported 9 cases operated upon for rectal cancer; all of the lesions were located below the peritoneal level. An earlier operative removal of the distal 1½ inches of rectum, attributed to Faget by Lisfranc, was performed in 1739 for an inflammatory lesion.

Lisfranc recommended surgical therapy for rectal lesions which were palpable by digital examination but resistant to other treatment. Infiltrating tumors were considered suitable for surgery, but fixation made surgical benefit doubtful.

The technique of operation described by Lisfranc included an oval perianal incision, made about ¾ inch from the anal border. In low-lying lesions, the distal tumor-containing portion of the rectum was pulled down, freed by blunt dissection, and amputated. A finger was inserted into the anus to allow traction. Traction permitted amputation of about 2 inches of lateral and posterior rectum with little dissection.

When higher lesions were excised, caution was necessary to avoid entering the peritoneum. The anal-peritoneal distance (anteriorly and laterally) was noted to be 6 inches in the female but only 4 inches in the male. Blunt dissection was used in separation of the rectum from the vagina or the prostate gland. In the female, traction exerted with one finger in the rectum and another in the vagina helped avoid inadvertent entrance into the vagina during dissection. The rectum was amputated subperitoneally. Blood vessels were ligated before the rectal stump was allowed to retract. Packing of the wound was employed as a hemostatic measure; the packing was removed within a few hours to permit free drainage.

Of the 9 patients reported by Lisfranc, six survived operation and left the hospital. Three patients died of complications of operation: one on the third postoperative day of peritonitis, another on the fourth day of "posterior space" infection, and the third on the twenty-fifth postoperative day of pelvic vein inflammation.

Lisfranc concluded: "Operative results should improve now that early diagnosis is possible and earlier lesions can be operated upon."

For 40 or 50 years following this somewhat optimistic prediction, however, the frequent occurrence of postoperative sepsis produced an almost prohibitive operative mortality. Mortality reportedly reached 80 per cent or higher. Surgical excision was not often recommended in the therapy of rectal cancer.[3, 4]

In 1873 Verneil revived interest in surgical treatment of rectal cancer. The Lisfranc operation was modified by adding excision of the coccyx to facilitate exposure: a circular incision made around the anus was continued posteriorly to the sacrococcygeal articulation; the coccyx was excised. The rectum was removed with minimal perirectal tissue; the bowel was divided close to the upper border of the tumor.

Kocher in 1875 introduced an improved operation for rectal cancer. To prevent gross contamination of the wound, a purse-string suture was utilized to close the anus at the beginning of the procedure. The scope of operation was also somewhat more extensive; aseptic technique allowed opening the peritoneum from below and more adequate mobilization of the upper rectum. Bowel continuity was re-established by bringing the pelvic colon down to the anus. The Kocher operation was a resection (in the German sense of the word) with division of the rectum close to its wall and without removal of perirectal tissues, levators, or anus.

The Kraske[6, 7] technique, introduced in 1885, permitted more adequate operative exposure. Although this method differed little from that of Kocher, exposure, especially of the posterior relations of the rectum, was facilitated by removal of the lower sacrum in addition to the coccyx. Intestinal continuity was preserved by suturing the pelvic colon to the anus.

Professor Gerota of Bucharest,[2] in 1895, published studies of the lymph nodes and lymph vessels of the rectum. Although earlier investigators had demonstrated the rectal lymphatics, Gerota described and clearly pictured the pararectal lymph nodes and the lymphatic collecting trunks. Few investigations of rectal lymphatics made since that time have done other than to repeat his studies and his results.*

Gerota divided the rectum into three areas, each with relatively different lymphatic drainage. The first, the "inferior region," is more properly not the rectum and corresponds to the skin at the anal margin. The second or middle region is the anal canal, limited below by the circumanal skin and above by the pectinate line. The superior region extends superiorly from the anal mucous membrane and includes all of the true rectum.

Lymphatic capillaries are present in three relatively separate networks, one mucosal, the second submucosal, and the third muscular. Each network communicates with the others.

The collecting trunks of the rectal lymphatics are of especial interest. The inferior region, the perianal skin, gives rise to three or four trunks on each side. These trunks pass to the lymph nodes in the inguinal region. Gerota's detailed studies indicate that the collecting trunks of this inferior region usually terminate in the superointernal group of the inguinal lymph nodes.

The lymphatics of the middle area of the rectum exhibit several pathways of lymph drainage. Anastomotic connections between the vessels of the several routes are frequent. Collecting lymphatics ascend in the columns of Morgagni to join the lymphatic networks of the superior area of the rectum. Other collecting vessels perforate the rectal wall just superior to the levators and traverse the pararectal lymph nodes, joining the collecting trunks from the superior region. The most striking route, however, is composed of those collecting vessels which pierce the wall of the rectum above the levators to pass to lymph nodes which follow the course of the middle hemorrhoidal arteries.

*It may be noted that Gerota's studies were carried out during an era in which inflammatory lesions of the anal and perianal regions were relatively more troublesome surgical problems than they are today; thus, considerable emphasis was laid on the details of the lymphatic drainage of these areas.

The collecting trunks of the superior region traverse the rectal wall in numerous places, frequently following the courses of blood vessels. After passing through the muscular layers of the rectal wall, most of the collecting trunks enter pararectal nodes of Gerota. Lymphatic drainage then continues superiorly and slightly posteriorly, to nodes in the mesorectum or terminal pelvic mesocolon.

The pararectal lymph nodes, "Gerota's glands," are located on the muscular layer of the rectum, deep to the fibroserous rectal coat. They are described as varying from four to seven in number; the most inferior is located just above the levator muscles. It is worthy of emphasis, however, that the true regional nodes of the lymphatics of the superior lymphatic region of the rectum are pictured by Gerota as those nodes grouped around the superior hemorrhoidal artery.

Thus, Gerota's investigations indicated that: (1) In the perianal skin, lymphatic drainage of inflammatory products or neoplastic material passes to the inguinal lymph nodes. (2) In the anal canal, lymph drainage may traverse the rectal wall to the regional lymphatics which follow the middle hemorrhoidal arteries, or may join the lymphatics of the so-called superior segment of the rectum by entering the anastomotic capillary lymphatic networks or by entering the pararectal lymph nodes. (3) In the rectum proper, or the superior segment of lymphatic drainage, the usual route of lymphatic drainage follows the collecting trunks through the rectal wall, hence to the pararectal lymph nodes, and then to the regional nodes along the superior hemorrhoidal artery. In addition, the numerous anastomoses between the lymphatics of this area and the middle rectal area doubtless help determine routes of lymphatic drainage by way of middle hemorrhoidal nodes.

Other investigations have helped to clarify rather precisely the usual and the potential routes of lymphatic drainage of the rectum. Studies of Poirier and others[16] confirmed the concept of the superior hemorrhoidal artery lymph nodes as the regional nodes of the rectum proper, and helped clarify the further pathways of drainage. Nodes forming the next glandular relay are located on either side of the origin of the inferior mesenteric artery at the aorta, and have been called the pre-aortic lymph nodes. Efferent vessels then pass to the retroaortic nodes located in the area anterior to L_3 and L_4 vertebrae, and then to the receptaculum chyli.

Studies have also emphasized the importance of the collateral and anastomotic lymphatic channels in this region. Morau[14] in 1894 concluded after investigation of the vaginal and rectal lymphatic systems: "Thus, not only is there contiguity between the lymphatics of the vagina and the rectum, but there is also continuity."

Cuneo and Marcille[16] studied and systematized the arrangement of the lymphatics of the prostate gland in man. The interrelation between the lymph drainage of the rectum and the prostate is emphasized by their employment of the identical engraving (Figs. 63 and 68) to illustrate both the lymphatics of the "middle region" of the rectum and those of the prostate gland. Investigations of Cuneo and Marcille point out that not only do the lymphatics of these

two regions, for the most part, terminate in identical lymph nodes (the hypogastric group), but lymphatic vessels passing from the prostate gland cross the lateral surfaces of the rectum. Further studies by the same investigators emphasize the continuity of the prevesical lymphatic network with the network which surrounds the prostate gland, the seminal vesicles, the vasa deferentia, and the terminal parts of the ureters.[18]

The studies of Gerota and others, which appeared about that time, were followed by a change in the philosophy of rectal cancer surgery by prominent Central European surgeons. Krönlein,[8] at the Berlin Congress of 1900, for example, expressed the conclusion that extirpation* rather than resection is the method of choice in treatment of rectal cancer, "in spite of some worsening of over-all functional results."

In discussion of Krönlein's address, Hochenegg[4] stated that, if total rectal extirpation, including rectum and flexure, were not to be done, then the limits of surgical success would be reached and better operative results would have to depend on earlier diagnosis.

Kraske[7] emphasized that to allow optimal success in extirpation, ". . . we must be still more radical: I believe that this leaves only one way and that is the method of the combined operation, a combination of either the sacral or perianal approach with the abdominal operation." In this regard it may be noted that Kraske's revised operation for rectal cancer, described in 1900, included ligation of the superior hemorrhoidal artery through the abdominal route.

Krönlein[8] reported results of 881 operations for rectal cancer in a collected series of excisions performed during the preceding 25 years by Kocher, König, Czerny, Krönlein, Gussenbauer, von Bergmann, Madelung and Garre, Kraske, Küster, Hochenegg, and von Mikulicz. The 3-year survival rate was 14.8 per cent, for the 640 cases for which data were available.† Operative mortality was 19.4 per cent. Of the operative deaths, 52 per cent were attributed to sepsis or peritonitis, 20 per cent to cardiac disease, 13 per cent to lung disorders, and 15 per cent to other causes.

The combined approach in rectal cancer surgery, endorsed by the 1900 Berlin Congress, however, was not entirely new. Czerny is credited with the first employment of the technique in 1884, and Volkmann reportedly used the combined approach for rectal cancer about the same time. Quenu,[17] in 1897, described a technique of operation utilizing a combination of the abdominal with the perineal or sacral route in the excision of rectal cancer. He observed that two essentials for successful operation are: (1) adequate exposure for complete excision of the lesion, and (2) protection of the wound against contamination by avoidance of incision into the rectum.

In 1897 Quenu reversed an earlier opinion that fixation of rectal tumor to the prostate gland precludes resection; inflammation, neoplastic invasion of the prostatic capsule, and actual invasion of the gland proper were noted to result

*Wide excision of the rectum and perirectal tissues as contrasted with the older "resection" or removal of only the rectum proper.

†Krönlein did not deduct operative deaths in his calculation of survival rates; when this deduction is made, the 3-year survival rate becomes 19 per cent, and in Kocher's 35 cases becomes 40 per cent.

in apparent fixation. When indicated, Quenu did not hesitate to excise a portion of the prostate gland as well as the seminal vesicles. He advised placing a catheter to avoid excision of the urethra, but predicted that future rectal cancer surgery could well include total prostatectomy with anastomosis of the urethra to the bladder.

Quenu emphasized that the critical area in excision of rectal cancer was often the anterior rectal-prostate or vaginal area. Lymph nodes lying on the posterior aspect of the rectum could be adequately excised with the exposure afforded by the Kraske technique, although Quenu considered coccygeal excision to be usually sufficient in this regard. More adequate exposure of the anterior relations of the rectum than could be afforded by coccygeal or sacral resection, however, appeared necessary to assure prevention of accidental opening of the rectum in the region of the prostate gland or the vagina, with consequent contamination of the wound with stool or with neoplastic cells.

Meanwhile, British surgeons were employing the Harrison Cripps and Allingham operations. Both are limited infraperitoneal excisions quite similar to the original Lisfranc operation and are characterized by ease and rapidity of execution.

Professor Miles,[12] as house surgeon at St. Marks Hospital, observed that, although the operative mortality with the Harrison Cripps and Allingham operations was low, cures were rare. Miles began a series of modifications of the Lisfranc-Harrison Cripps-Allingham technique by adding coccygeal excision. Of 9 patients operated upon with this method (1899 to 1901), each had early recurrence of tumor.

A second modification of operation added a preliminary colostomy to the procedure. Of 15 cases (1902 to 1904), all but one had prompt recurrence. A third operative modification added to the tissues excised: perianal skin, ischiorectal fat, fascia propria recta, terminal mesocolon, levators ani, and pelvic peritoneum; the bowel was divided 2 inches above the rectosigmoid junction. This technique, employed in 13 operations (1904 to 1905), produced a single survivor. One operative death occurred. A fourth series added to the previous technique "several inches of pelvic mesocolon." Of 18 patients, all but one had early recurrence.

Miles studied the factors seemingly responsible for the failures associated with the four modifications of technique. Autopsies of patients dead of carcinoma showed that residual or recurrent tumor was often present in the pelvic peritoneum, pelvic mesocolon, and in lymph nodes located in the region of the common iliac artery bifurcation. Miles concluded that an adequate operation for rectal cancer should include: (1) an abdominal anus; (2) removal of all of the pelvic colon; (3) excision of the pelvic mesocolon below the crossing of the common iliac artery, and a strip of peritoneum "at least one inch wide on either side of it"; (4) removal of the group of lymph nodes over the bifurcation of the common iliac artery; and (5) carrying out the perineal portion of the operation as widely as possible.

It is of interest to note that the earlier procedures of Miles, although somewhat limited in scope, would seem to have been potentially capable of allowing complete excision of lesions which were actually confined to the rectum proper. In 57 operations, however, only 3 patients survived 6 months to 3 years postoperatively.[13] Thus, most of the patients treated by Miles' earlier limited techniques of excision apparently had quite advanced disease, since all but 5 per cent either died or had recurrence of tumor within the short period of follow-up.

In December, 1908, Miles published the technique of his one-stage abdominal perineal operation, employing these principles, including a report of the first 12 patients operated upon by the described technique. Of the 12 patients, 5 operative deaths occurred. One of 3 female patients and 4 of 9 males failed to survive. The causes of death were "hypostatic congestion of the lungs" in one patient, a strangulated knuckle of small intestine in a pelvic floor hernia in a second patient, gangrene of the colonic stump below the colostomy in another, and peritonitis in 2 patients.

The most serious detriment to early widespread adoption of the Miles technique, in addition to the recurring objection to loss of the "anal anus," appears to have been the relatively high operative mortality initially observed. The 40 per cent rate which followed the first of these operations was twice that noted with the Kocher-Kraske-Krönlein techniques of the same period, and was substantially greater than that seen with the less radical Harrison Cripps or Allingham excisions. Factors responsible for the substantial operative fatalities included the frequent occurrence of shock during and shortly after operation. The cause of shock with this more extensive excision likely was often the same as that pointed out earlier by von Bergmann[20] in comment on the Kraske and Hochenegg operations of 1900—bleeding.

The initially high operative mortality associated with the Miles procedure was met in a variety of ways. Interest in more limited surgical excision was revived. In 1920 Lockhard-Mummery[10] described an operation designed to "remove the rectum for cancer with reasonable degree of safety without the serious mortality which has hitherto accompanied rectal excision." The chief merit of this technique appears to lie in the low operative mortality, especially when applied to debilitated patients. Although stated to be ". . . suitable in any case where the growth is at the anus or anywhere in the rectum proper, provided that it is not fixed to important structures . . . ," the limited scope of the Lockhard-Mummery excision makes small, indeed, the potentiality of cure for any but early lesions.

To reduce operative mortality, candidates for the Miles operation were selected somewhat more critically. Patients who presented increased risks were often excluded. Miles cautioned against application of his operation to patients with tumor spread beyond the scope of resection and carefully evaluated cardiorespiratory status before operation. A corresponding decrease in operative mortality took place as resectability rates decreased. Mayo[11] observed in this regard, " . . . if the operability is high in a given clinic, the mortality will be high."

Instrumental in some reduction in operative mortality was the introduction of the staged procedure in the technique of performance of the abdominal perineal operation.[5] The abdominal portion of the operation, including the colostomy, was often performed as the first stage; the perineal excision was done at a later stage. In cases where cure was found to be unlikely, the second stage could be omitted.

During the 50 years since the introduction of the Miles operation, with the gradual improvement of anesthesia and of therapy for hemorrhagic shock, "hypostatic congestion of the lungs," and operative shock have become less frequent direct causes of hospital deaths. Ten years after Miles' report, operative deaths were 20 to 36 per cent. In 1925 the French Surgical Congress on rectal cancer reported an average operative mortality of 20 per cent.[15] By the 1930's, 80 to 90 per cent of patients survived operation. The hasty operations of the early era have become less necessary, and attention could be directed to atraumatic and aseptic operative techniques. Today, sepsis and shock, two serious complications tending to justify limited excision in the bygone years, have been largely controlled, and abdominal perineal excision can be done with an operative mortality well under 10 per cent.

Resectability rates for carcinoma of the rectum with the abdominal perineal operation have gradually increased. Decreased operative complications and fewer hospital deaths during the past several years have allowed poorer-risk patients to undergo operation. As late as 1942, however, David and Gilchrist[1] classified patients who were over 65 years of age, obese, pregnant, or who had coronary heart disease as "questionable" candidates for surgery; a 9.5 per cent operative mortality was associated with this group (105 patients), contrasted with a 4.3 per cent mortality rate in 74 "favorable" cases.

Palliative excisions of rectal lesions, performed even in the presence of unresectable spread of tumor, have allowed increased resectability rates and greater palliation for many patients with "incurable" cancer. Preoperative preparation, postoperative care, more adequate operating room facilities, and decreased fear of surgery, have also contributed to increased resectability and lessened operative mortality over the past half-century.

The greatest volume of debate in regard to the Miles operation during the past 50 years has seemingly concerned the precise definition of conditions under which the operation should be employed. The initially observed high operative mortality, incident to the magnitude of the procedure and tending to preclude application of the operation to poorer-risk patients, has largely been conquered. The risks of sepsis and shock are no longer prohibitive. Today, the chief factor in the restriction of application of the abdominal perineal excision in favor of the more limited and less adequate operations often appears to be the alleged "multilation" inherent to the procedure: it must be conceded by even the most enthusiastic advocates of the Miles operation that patients who undergo this procedure will never again defecate by the normal route.

Sentimentality regarding the mode of defecation, however, probably should play no part in choice of appropriate curative operative procedure for the patient with carcinoma of the true rectum. A recent study of patients with

rectal cancer, involving more than 500 cases and extending over a 15-year period with 100 per cent follow-up, presents little doubt as to the superiority of the abdominoperineal excision.[3] Statistically valid data indicate that only the earliest lesions (Dukes A) of the true rectum allow a choice of excision procedure. The more advanced cases (Dukes B and C) necessitated an abdominoperineal excision for any appreciable possibility of long-term, cancer-free survival.

Proposals favoring routine employment of sphincter-saving or other less comprehensive procedures would appear to merit only passing and historical note, with the exception of application to those selected cases with Dukes A lesions. Further betterments in surgical results could be expected to follow: (a) extension rather than restriction of the adequacy of excisional scope, and (b) increase in percentage of patients with Dukes A lesions undergoing curative excision procedures.

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